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Preface

Pediatric Urology for the General Urologist

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Guest Editors

When tasked with assembling appropriate topics for an issue of the *Urologic Clinics of North America* on pediatric urology, we asked ourselves, ''What topics would we most like to be updated?'' The difficulty is choosing between the latest research findings or treatment controversies, and we think the previous Guest Editors, George Kaplan, MD, and Edmond Gonzales, Jr, MD, hit the nail on the head. The topics covered in this issue are broad and common to everyday practice, not just rare entities. However, enough great advances have occurred in pediatric urology since the last issue 9 years ago that each subject seems fresh and relevant. It is equally as important for a urologist to have the knowledge needed for an in-depth prenatal visit for severe bilateral hydronephrosis as it is for isolated distal hypospadias.

Our group of exemplary authors takes us on a journey from the prenatal evaluation and treatment of the hydronephrotic fetus to the latest recommendations for pediatric urologic oncology. Carr initially explores the prenatal management of urologic problems, including the latest invasive techniques. A bevy of authors then ably tackle the complex urogenital disorders of neonates: prune belly syndrome and posterior urethral valves (Strand), exstrophy (Kiddoo, Carr, Dulczak, and Canning), myelomeningocele (Snodgrass and Adams) and intersex (Hyun and Kolon). Each author provides an insightful approach to the diagnosis of these problems along with a state-of-the-art treatment plan that can be practiced by any urologist in a private or academic setting.

The next three articles cover the ''bread and butter'' of pediatric urology. Shukla, Patel, and Canning describe the various techniques and tricks of hypospadias repair; Hutcheson very aptly covers the ever-controversial circumcision; and Kolon, Patel, and Huff delve into the diagnosis and treatment of the undescended testis.

Our next group of authors succinctly describes how we should handle a continually vexing problem: the unstable pediatric bladder. Schulman provides insight into voiding dysfunction; Mammen and Ferrer then describe the medical management of nocturnal enuresis, while Blum addresses behavioral treatment of the same disorder.

Bong and Koo educate us on the adolescent varicocele—a topic that appears to require a slightly different approach than in the infertility patients seen as adults. Urinary tract infections and vesicoureteral reflux are two extremely common diagnoses that seem to be more perplexing and difficult to understand and treat as the years go by. Ma and Shortliffe, Malhotra and Kennedy, and Cooper and Austin present these topics in a manner that is easy to understand.

Meyers concisely describes a thoughtful approach to hematuria in children. Likewise,

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Bartosh admirably instructs us how to medically manage our stone patients in an effort to keep them out of the operating room once we clear their initial process. Finally, Wu and Docimo provide an excellent review of the surgical treatment of stones, and Peters shows us the future of urology with a journey through laparoscopy and robotics.

Oncology is the one section of pediatric urology that can be both extremely rewarding and terribly discouraging. Zderic discusses the treatment of renal and adrenal tumors, while Wu and Snyder outline the latest therapy for bladder, prostate, and testis neoplasms.

All of the authors deserve a hearty thanks for their thoughtful and prompt submissions. We would like to express our gratitude to Sharon Brown for cheerfully accepting the laborious secretarial task of putting this issue together. We would also like to thank Catherine Bewick and her staff at Elsevier Science for their ever-cheerful and invaluable assistance. We sincerely hope that this issue of the *Urologic Clinics of North America* will be helpful in daily pediatric urology management and continues the fine tradition of education that this series has provided.

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Prenatal management of urogenital disorders

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The incidence of reported structural abnormalities detected by antenatal sonography is 1% [1]. Nearly 50% of these anomalies involve the central nervous system, 20% are genitourinary, 15% are gastrointestinal, and 8% are cardiopulmonary. The recognition of these urologic abnormalities by prenatal ultrasonography affords an opportunity to assess the natural history of certain conditions, allow for a prenatal diagnosis in other situations, and potentially alter the course of the congenital process by in-utero intervention. The ability to detect urogenital abnormalities depends on the skill and experience of the sonographer, and usually is better late in gestation, when the fetus is larger and an anomaly is imaged readily [2]. Hydronephrosis is the urogenital anomaly most often detected, suggesting that an obstructive process may be present. Other etiologies for hydronephrosis include vesicoureteral reflux, multicystic dysplastic kidney, and certain abnormalities of the ureteropelvic junction and ureterovesical junction [3].

Abnormalities involving the genitourinary tract may be suspected in as many as 1 in 100 pregnancies, depending on the sonographic criteria [4,5]. The degree of hydronephrosis and the gestational age may help indicate whether an obstruction is present and the ultimate need for surgical intervention [6]. For instance, an anterior-posterior diameter of greater than 10 mm in a fetus 30 or more weeks' gestation increases the likelihood of subsequent surgery being required [7].

Advances in fetal diagnosis and treatment have made fetal intervention not only possible but routine. Therapy such as in utero transfusion techniques for treatment of erythroblastosis fetalis, the initiation of pharmacologic treatment of cardiac arrhythmias [8,9], and the introduction of percutaneous fetal drainage catheters [10,11] for hydrothorax were devised initially. Correction of more complex anatomic defects (eg, diaphragmatic hernia) necessitated more invasive procedures involving direct fetal exposure and surgical repair [12–15].

Because hysterotomy for fetal surgery posed obvious maternal risk, the fetal surgery team at the University of California at San Francisco (UCSF) thought that open fetal surgery should not be attempted until: (1) the natural history of the disease was established by following up untreated cases; (2) selection criteria for cases requiring intervention were developed; (3) the pathophysiology of the fetal disorder and the correction was defined in animal models; and (4) hysterotomy and fetal surgery could be performed without undue risk to the mother and her reproductive potential [15].

Early results from the fetal treatment program at UCSF included 17 patients with one of four fetal anomalies: severe bilateral hydronephrosis (seven cases), congenital diaphragmatic hernia (eight cases), sacrococcygeal teratoma (one case), and congenital cystic adenomatoid malformation. Of the seven fetuses with bilateral hydronephrosis, two neonates died at birth with pulmonary hypoplasia, one died of septicemia with normal renal function at 9 months of age, and two are alive and healthy, although renal deterioration has occurred in one patient. One fetus was removed because of inadequate repair of a coexisting cloacal anomaly and one was delivered 12 days postrepair when the mother decided to discontinue tocolytics [15].

The early experience reinforced the notion that selected anomalies can be treated effectively only

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by direct hysterotomy and open fetal surgery. This approach can be justified only if the risk to the mother's health and reproductive potential is acceptable. Concerns with maternal risk focused on three areas: (1) the operative risk of general anesthesia and a midgestation hysterotomy; (2) the risk for premature labor following hysterotomy; and (3) the risk for compromising future reproductive potential [15]. The biggest challenge recognized was the ability to control the uterine contractions after hysterotomy. Despite maintaining oral tocolytic therapy, all of the women developed preterm labor ranging from 25 weeks' to 35 weeks' gestation. In addition, women who have undergone successful interventions are committed to giving birth by caesarian section; that is, two hysterotomies during one pregnancy. The fetal therapy team at UCSF cautioned that the ability to perform these procedures does not mean that they should be done. The team further added that it is critical to examine vigorously the efficacy, safety, and cost-effectiveness of developing fetal therapies compared with conventional treatment. These sentiments ring true today.

Box 1. Causes of antenatal hydronephrosis

- Anomalous ureteropelvic junction/ureterovesical junction obstruction
- Multicystic kidney
- Primary obstructive megaureter
- Vesicoureteral reflux[a]
- Ectopic ureterocele[a]
- Ectopic ureter
- Physiologic dilatation
- Posterior urethral valves[a]
- Prune belly syndrome[a]
- Urethral atresia[a]
- Hydrocolpos[a]
- Pelvic tumor[a]
- Cloacal anomaly[a]

[a] Bladder may be distended.

Antenatal hydronephrosis

When a fetus is identified with a suspected urinary tract abnormality, the goals of management include determining the differential diagnosis, assessing associated anomalies, and determining the fetal and postnatal risk of the anomaly. Hydronephrosis is recognized by demonstrating a dilated renal pelvis and calices. In addition, the ureter and bladder may be dilated. The later the sonogram is performed, the more likely an existing abnormality will be detected because of the increase in renal pelvic diameter in the face of obstruction [2].

Box 1 lists the differential diagnosis of antenatal hydronephrosis [16]. Many of these conditions may cause bilateral hydronephrosis. A distended bladder suggests bladder outlet obstruction, such as posterior urethral valves or a large ectopic ureterocele, but fetuses with prune belly syndrome or high-grade vesicoureteral reflux also may have bilateral hydronephrosis with a distended bladder [17,18]. Careful screening for other congenital and chromosomal abnormalities is necessary because these commonly can be associated with urologic anomalies.

The primary considerations in determining fetal management include overall fetal well being, gestational age, whether the hydronephrosis is unilateral or bilateral, and the volume of amniotic fluid present. In the face of unilateral hydronephrosis, no specific fetal therapy is necessary. The development of an in-utero ureteropelvic junction obstruction may compromise the renal function, depending on the timing and severity of the obstruction. On the other hand, the neonatal kidney has a tremendous capacity for improvement in function following pyeloplasty [19]. Even the in-utero case of bilateral ureteropelvic junction obstruction (bilateral hydronephrosis and normal bladder) rarely will compromise amniotic fluid volume and pulmonary development. Thus, specific interventions, including percutaneous drainage of the fetal kidney or early delivery to allow immediate urologic surgery, are unwarranted. The same can be said of nonintervention for primary obstructed megaureters.

The primary life-threatening congenital urologic anomalies, which are characterized by bilateral hydroureteronephrosis and a distended bladder that does not empty, include urethral atresia, prune belly syndrome, and posterior urethral valves. Progressive renal deterioration in utero will compromise amniotic fluid production and lead to pulmonary hypoplasia [20], which can be the lethal factor. Urethral atresia, as a result of the severity of the obstruction, is nearly always fatal because of the underlying renal dysplasia and associated pulmonary hypoplasia. Prune belly syndrome generally is considered nonobstructive, but this condition can lead to renal insufficiency

postnatally. Prenatal management of presumed posterior urethral valves that are compromising renal function and ultimately urine production depends on establishing drainage between the fetal bladder and the amniotic space [21], including placement of a vesicoamniotic shunt, creation of a fetal vesicostomy or pyelostomy, or percutaneous urethral valve ablation through a mini-scope [22,23]. Early efforts in managing such fetal patients involve identifying parameters that would predict outcome in these difficult cases. Several perinatalogy groups reported unfavorable prognostic factors including: (1) prolonged oligohydramnios [24,25]; (2) presence of renal cortical cysts [26]; (3) urinary sodium 100 mEq/L or more, chloride more than 90 mEq/L, osmolarity more than 210 mmol/L, and elevated urinary β2-microglobulin (greater than 6 mg/L) [27–30]; and (4) reduced lung area and thoracic or abdominal circumference [31].

The variability of gestational age at the onset of an obstruction, differences in the underlying cause for the obstruction, and the few clinical trials make comparing interventions difficult, and may explain in part why the promise of experimental studies often has not translated into clinical practice.

Therapeutic options

The mainstay for fetal treatment of posterior urethral valves involves urinary diversion, usually with a vesicoamniotic shunt. Previously, attempts at open surgery to create a vesicostomy or pyelostomy had been abandoned, but direct valve ablation in utero using an endoscopic approach suprapubically has been used at several centers. The obvious benefits are avoiding the high complication rate of shunting and allowing the bladder to fill, empty, and resume normal development.

Vesicoamniotic shunting

Vesicoamniotic shunting is performed with ultrasound guidance using a pigtail shunt (Rocket Medical, Washington, England; Cook Urological, Spencer, Indiana) (Fig. 1). A double pigtail is positioned with one end in the bladder and the other end in the amniotic space. Color-flow Doppler imaging allows visualization of the umbilical arteries, which course laterally to the fetal bladder. When oligohydramnios exists, amnioinfusion is performed to allow a potential space in which to place the intra-amniotic end of the catheter.

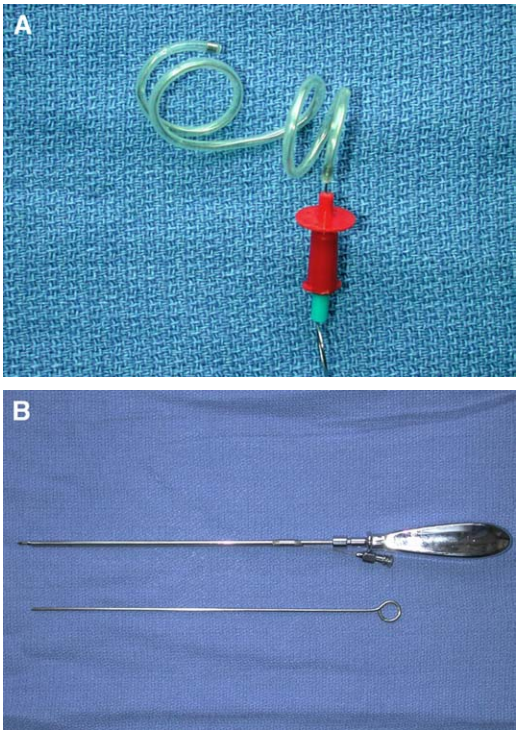

Fig. 1. Double-pigtail fetal bladder-drainage catheter (*A*) used through a trocar (*B*) is placed percutaneously using color-flow Doppler imaging.

Technical considerations

Technical considerations with vesicoamniotic shunting involve low placement of the shunt into the bladder to prevent displacement following bladder decompression. The optimal site for trocar entry is midway between the pubic ramus and the insertion of the umbilical cord.

Outcome

Several series have reported on their experience with prenatal intervention using vesicoamniotic shunting, as summarized in Table 1. The overall perinatal survival after intervention was only 47%, and shunt-related complications occurred in 45% of cases. End-stage renal disease was seen in 54% of cases [32] and 56% of fetuses with oligohydramnios did not survive. Failure to restore amniotic fluid volume was associated with 100% mortality. In cases with poor urinary prognosis, postnatal renal insufficiency was noted in 87.5% of survivors, and where intervention improved the chances of survival, it did not alter the renal outcomes. Limiting the intervention to those with

Table 1
Reports of vesico-amniotic shunts

Author	No. of patients	No. of survivors	Oligo hydramnios	Normal renal function
Elder and colleagues	21	9	9	1 (11)
Crombleholme and colleagues	19	12	17	7 (58)
Manning and colleagues	87	35	69	16 (59)
Lipitz and colleagues	124	6	13	0
Freedman and colleagues	28	17	28	12 (70)
Holmes and colleagues	14	8	14	3 (37)

good prognosis improves survival and lowers incidence of renal failure [33].

Crombleholme and colleagues [27] and Freedman and colleagues [34] evaluated outcomes based on prognosis as determined by fetal urine biochemistry. Fetuses with oligohydramnios were separated into those with dysplasia and those with normal renal function. Poor renal function was confirmed in 14 to 16 cases (88%) that were shunted successfully, indicating that diversion rarely preserves or ameliorates function in this subset. The underlying dysplasia is not reversed with successful intervention. In contrast, 85% of survivors with a good prognosis had normal renal function. When amniotic fluid returned to normal, pulmonary function was preserved, as has been demonstrated in animal studies [33].

Complications

The early experience with vesicoamniotic shunting was associated with significant complications, including shunt blockage, shunt migration, preterm labor, urinary ascites, chorioamnionitis, and iatrogenic gastroschisis [35,36]. In addition, there are times when shunting is not technically possible or is associated with significant intraprocedural complications [32]. The fetal surgery registry documented that only 10% of shunts were placed successfully in various centers during the 1980s. The most significant maternal complication of percutaneous intervention was infection. Maternal life-threatening infections associated with fetal loss were reported in 3 of 159 cases [33]. Finally, Quintero and colleagues [37] reported on at least seven intrauterine deaths believed to be caused by shunt placement.

Mechanical complications include shunt displacement from the fetal bladder, often as a result of a fetal extremity becoming entangled in the distal intra-amniotic segment of the shunt, with subsequent physical displacement of the proximal end out of the fetal bladder. This can result in significant urinary ascites as urine flows through the iatrogenic defect in the bladder wall. This ascites occasionally can lead to massive fetal abdominal distention, diaphragmatic elevation, intraabdominal and intrathoracic hemodynamic changes, and subsequent development of hydrops. Shunts may have to be placed in the fetal abdomen to drain urinary ascites until the defect in the bladder wall heals. Ultimately, reshunting may be necessary when the defect is healed [33].

Fetal cystoscopy

The direct valve approach may obviate some of the complications of shunt placement and restore the bladder to normal. In addition, direct visualization will confirm the etiology of lower urinary tract obstruction. Quintero and colleagues [37] first described this technique in the management of fetal obstructive uropathy under maternal general anesthesia. The indications are similar to those for vesicoamniotic shunting, with a midgestation pregnancy at 17 to 20 weeks being optimal.

Technical considerations

Fetal cystoscopy is performed best by the fetal medicine and urologic teams jointly. The fetal cystoscope is introduced through a 14-gauge trocar and cannula through the maternal abdomen, uterus, and fetal abdomen into the fetal bladder under ultrasound guidance and antibiotic coverage following local anesthetic infiltration [33].

As opposed to shunt placement, the fetoscope must enter the bladder through the dome so that it can be directed downward in a straight line with the urethra. Color-flow Doppler imaging helps delineate vascular structures. The fetoscope used currently is the Storz (Carl Storz, Tuttlinger, Germany) 1.3-mm outer diameter, 1-mm lens diameter, semirigid embryo-fetoscope with a 0° angle of view and 70° field of view. Upon entry into the fetal bladder, aspirated urine is sent for

electrolyte analysis and inspection to note presence of bladder trabeculation and hemorrhage. The fetoscope is advanced carefully into the prostatic urethra following visualization of the trigone and bladder neck to appreciate the site of obstruction. Posterior urethral valves appear as a membrane arising from the verumontanum. Once the presence of posterior urethral valves has been confirmed, laser ablation is performed using a 400- to 600-μm YAG laser fiber, in which 30 to 40 W of successive 0- to 2-second pulses are used to ablate the valves [38]. Direct contact with the valves will achieve a more intense effect in a smaller zone of tissue so as to ablate only the valves and not surrounding tissue. Other techniques that have been experimented with include saline injection to disrupt the membranous valves or insertion of guidewire through the valves to disrupt them mechanically.

Successful ablation can be documented by placing the color Doppler-imaging probe over the amniotic cavity and injecting fluid into the bladder; a color Doppler signal seen in the amniotic space indicates successful ablation.

Outcome

The initial series reported by Quintero and colleagues [37] included nine fetuses who underwent fetal cystoscopy and laser ablation of the valves. Urethral patency was only present in four fetuses. In those with a patent urethra, two were viable at birth, one had progressive renal damage and was aborted, and two were lost to chorioamnionitis. The two successful cases ultimately died, one at 4 months of age from bronchopneumonia and the second at 3 months of age from necrotizing enterocolitis.

Agarwal and colleagues reported on 11 fetuses between 16 and 24 weeks' gestation who had fetal cystoscopy [33]. There were no immediate or long-term iatrogenic complications from the procedure. Five of the eleven cases developed postprocedural urinary ascites that was managed conservatively. Seven of the eleven cases were for diagnosis only, with the remainder undergoing therapeutic intervention with either hydroablation (N = 1) or guidewire technique (N = 3). Complete valve ablation was successful once. Two cases were believed to be partial successes (increase in amniotic fluid volume and decrease in bilateral hydroureteronephrosis during pregnancy), but required retreatment postnatally. Three of four infants had acceptable renal function.

The authors found the main challenge was in gaining access to the posterior urethra with the cystoscope. This vesicourethral angle can be difficult to negotiate and becomes more acute with advancing gestation. Even if the posterior urethra is entered, valves may not be visualized. These challenges limit the usefulness of the procedure. Further refinement of the fetoscopes, such as a curved trocar or flexible cystoscope, is being evaluated.

Current state of fetal intervention for obstructive uropathy

The current approach supports fetal intervention of the male fetus with suspected posterior urethral valves with good renal prognosis and oligohydramnios. The effectiveness of such an intervention has been questioned when the long-term outcome of fetal patients with posterior urethral valves from UCSF was reviewed. Of the 36 patients with favorable electrolytes and oligohydramnios treated by one of three methods over 18 years, 14 (39%) had posterior urethral valves, and only eight of these (57%) survived. Five of the survivors (63%) developed chronic renal impairment and five required urinary diversion/reconstructive procedures [39].

These outcomes imply that intervention may facilitate a viable infant at birth, but the sequelae of posterior urethral valves have not been reversed. An alternative approach would be to shift the emphasis from promoting survival of those who would otherwise die at birth from oligohydramnios-related lung hypoplasia toward relieving obstruction in utero from posterior urethral valves not associated with oligohydramnios. De-emphasizing intervention for life-saving fetal therapy and promoting quality of life–enhancing fetal therapy must be balanced with the high complication rate of shunting. The promise of successful endoscopic ablation of valves may mean that a well-timed, one-stage definitive treatment in utero can prevent renal tract sequelae of posterior urethral valves [38].

Fetal myelomeningocele repair

The success of dealing with potentially lethal conditions in utero has opened the door for correcting disorders that are not lethal, but cause considerable morbidity. In particular, myelomeningocele is the most common and severe form of spina bifida, affecting nearly 1 in 2000 infants born

alive. In addition to varying degrees of paralysis, individuals with myelomeningocele often have mental retardation, bowel and bladder dysfunction, and orthopedic disabilities. The hydrocephalus, Arnold-Chiari II malformation, and spinal cord tethering at the site of surgical repair lead to significant morbidity and mortality. Management of these individuals has involved termination of pregnancy following diagnosis or postnatal closure and a lifetime of supportive care.

Experimental work in various animal models proved that the fetal closure of the myelomeningocele arrests the continuing damage to the spinal cord as it is exposed to the amniotic fluid. This closure could preserve function of lower extremities, bowel, and bladder. Early experience with human fetal myelomeningocele closure showed that the Arnold-Chiari malformation and progressive hydrocephalous are arrested. Given the significant risk of prenatal intervention, the Center for Fetal Diagnosis and Treatment at Children's Hospital of Philadelphia offered this treatment with select criteria. The fetus had to have an Arnold-Chiari malformation, mild or moderate ventriculomegaly, normal leg movement, no apparent clubbing of the feet, normal karyotype, and no accompanying lethal anomalies. By limiting intervention to those with the Arnold-Chiari malformation, the infants most likely to suffer from hydrocephalus or life-threatening brain stem symptoms and to require frequent postnatal surgical intervention were being offered therapy. The spinal defect was closed between 21 and 25 weeks' gestation, using techniques similar to those of postnatal repair [40].

The early experience with such repair arrested hind-brain herniation, decreasing the ventricular shunting that was necessary with the Arnold-Chiari II malformation and hydrocephalus [41,42]. This exciting finding will require long term follow-up to determine whether neurologic function is improved. In addition, the incidence of clubbed feet and other orthopedic anomalies is expected to diminish, reducing the need for future surgical intervention.

Bowel and bladder function, which remain lifetime management issues, may be improved with successful in-utero repair of the myelomeningocele. Vanderbilt and UCSF have reported on the early urodynamic finding in this group of patients [43,44]. There have not been significant alterations in bladder function as were noted with neonatal urodynamic testing. These patients may have had their closure performed when arrest of the progressive spinal cord injury would not have been prevented (beyond 25 weeks' gestation). In addition, assessing bladder function solely on one early urodynamic study may be unfounded.

Recent work from Sillen and colleagues has shown a changing urodynamic pattern in healthy infants [45], premature infants [46], and toddlers [47]. Preterm infants' voiding pattern is characterized by an increased number of interrupted voidings as a result of the immature behavior of the detrusor-sphincter complex. The high number of voidings during sleep underscores the immature pattern for preterm infants. Healthy full-term infants will void an average of once per hour, but generally less than 10% of bladder capacity remains as mean residual urine. Preterm infants manifest an interrupted voiding in which complete voiding consists of two or three small voidings with an empty bladder only after the final voiding. By 2 years of age, the interrupted voiding pattern becomes rare. Voiding during sleep occurs mainly during the first 7 months of life but is seen rarely after 18 months of age. It will be mandatory to follow these children through their toilet-training years to understand the effects of the surgery.

The National Institute of Child Health and Human Development recently has funded the Management of Myelomeningocele Study trial, which will randomize fetuses who are diagnosed with myelomeningocele to either fetal repair before 26 weeks' gestation or postnatal repair. The design is to test the safety and efficacy of the surgery. The need for ventricular shunting is the primary outcome; secondary outcomes include the development of Arnold-Chiari malformation, neonatal morbidity and mortality, long-term neurologic function, maternal morbidity, and cost. Other important variables being assessed include locomotion, distal somatosensory function, bowel and bladder continence, and the need for subsequent surgical procedures. The three centers involved in this study, Children's Hospital of Philadelphia, Vanderbilt, and UCSF, will be able to compare directly patients with pre- and postnatal closure because the continuing testing of these patients will be performed at the respective centers. A supplemental grant is being proposed to follow these patients for at least 5 years to assess more accurately bowel and bladder issues.

Congenital adrenal hyperplasia

A girl with congenital adrenal hyperplasia often presents with ambiguous genitalia as a newborn,

with some infants developing life-threatening adrenal insufficiency. The most common enzyme defect is 21-hydroxylase deficiency, resulting in excessive levels of 17-hydroxy progesterone in the amniotic fluid. If the condition is recognized in utero, prenatal therapy can prevent the virilization of the female fetus by adrenal suppression. Appropriate therapy involves dexamethasone given daily to the expectant mother [48]. Because the virilization occurs early in the first trimester, the therapy needs to be instituted before the gender of the fetus is known (8 weeks' gestation). Subsequent chorionic villous sampling can be performed safely at 9 to 12 weeks' gestation so that appropriate measurements of amniotic fluid and direct DNA analysis of the 21-hydroxylase gene (*CYP21*) with molecular genetic techniques are performed. Once confirmed, the steroid treatment is continued for the duration of the pregnancy. If it is found that the fetus is an unaffected male or female, the maternal dexamethasone is discontinued. When properly administered, dexamethasone prevents ambiguous genitalia in the affected female and is safe for the mother and fetus [48].

The New York Hospital–Cornell Medical Center experience comprised prenatal examination for congenital adrenal hyperplasia owing to 21-hydroxylase deficiency in 403 pregnancies over the past 15 years. In 280 pregnancies, the diagnosis was made by amniocentesis; in 123, chorionic villous sampling was performed; and of late, the rapid allele-specific polymerase chain reaction was used for DNA analysis. Of the 84 fetuses were found to be affected with classic 21-hydroxylase deficiency, 52 were female, 36 of whom were treated prenatally with dexamethasone. Dexamethasone administrated before 10 weeks' gestation (23 affected female fetuses) reduced virilization. Overall, the average Prader score for affected females treated prenatally was 1.7 (including the partially treated). The average score for untreated affected females was 3.9 [49].

Box 2. Important objectives

1. The prenatal detection of hydronephrosis is common and can be caused by diverse etiologies, such as a ureteropelvic junction obstruction, multicystic dysplastic kidney, vesicoureteral reflux, or physiologic dilation.
2. The mainstay of prenatal therapy for bladder outlet obstruction caused by posterior urethral valves or urethral atresia is placement of a vesicoamniotic shunt to improve or maintain amniotic fluid volume.
3. The in-utero repair of myelomeningocele has decreased the need for postnatal ventriculoperitoneal shunting caused by hydrocephalus and ultimately may improve the neurologic function of affected individuals.
4. Congenital adrenal hyperplasia, often caused by a 21-hydroxylase deficiency, will lead to virilization of the female fetus. These effects can be negated by administering dexamethasone to expectant mothers before 8 weeks' gestation.

Summary

Fetal therapy has evolved over the past 20 years to include treatment for life-threatening or severely disabling malformations in which postnatal treatment is either too late or inadequate. Less-invasive basic procedures are being devised that could decrease the morbidity associated with open fetal surgery. In certain situations, early detection of medical conditions can allow successful in utero treatment and reverse or prevent devastating sequelae (Box 2). Finally, the prospect of prenatal gene therapy can have significant effects on inborn errors of metabolism such as lysosomal storage diseases, immunodeficiencies such as severe combined immunodeficiency syndrome, and hemoglobinopathies such as thalassemias and sickle cell anemia [40]. Continuing research efforts and well-controlled clinical trials that randomize patients to in-utero or postnatal therapy and carefully define and track long-term outcomes will be crucial to the success of such interventions.

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Initial management of complex pediatric disorders: prunebelly syndrome, posterior urethral valves

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Prunebelly syndrome (PBS) and posterior urethral valves (PUV) are conditions with impaired voiding proficiency caused by abnormal bladder development. Although infants with these conditions appear different, they may all present with respiratory distress, profound renal insufficiency, severe hydroureteronephrosis (HUN), and bladder wall thickening. Infants with PBS also exhibit bilateral intra-abdominal cryptorchidism and a characteristic lax abdominal musculature. The incidence of PUV (1 case per 5000 to 8000 male births) [1] is roughly five times greater than that of PBS (1 case per 29,000 to 40,000 male births) [2]. Histologic studies of fetal bladder specimens have demonstrated an increase in bladder muscle thickness in infants with both of these conditions, implicating early urinary tract obstruction in the etiology [3].

The ultimate pattern of detrusor dysfunction results from differences in the onset, severity, and duration of urethral obstruction in PBS and PUV. Urethral obstruction is thought to occur earliest in PBS, causing massive distension of the bladder followed by urinary ascites [4–6]. The severity and early onset of urethral obstruction in PBS promote extensive renal dysplasia, persistence of a patent urachus, and myogenic bladder failure (similar to the end-stage detrusor dysfunction evident in PUV [7]). Massive bladder distension and ascites combine to degenerate the abdominal wall muscles and prevent testicular descent. Rupture of the obstructing membrane just proximal to the membranous urethra [2] occurs most often before birth. These events account for the recognized spectrum of urethral profiles in PBS ranging from widely patent to stenotic [8]. Although urethral obstruction in PUV is persistently evident postnatally, a spectrum of severity exists. Another mechanism involving a primary mesodermal defect is also suspected in PBS, because fetal bladder histology ranges from thin muscle walls with increased collagen (no evidence of obstruction) to detrusor hypertrophy with a normal ratio of connective tissue (less severe but similar to the findings in PUV, indicating urethral obstruction) [3]. Abnormal banding of the ejaculatory ducts and agenesis of the seminal vesicles are found only in PBS (Fig. 1), further supporting a fundamental difference in the embryologic development of these two entities [8]. Genital duct abnormalities are detected when PBS presents in female infants [9–12].

Antenatal ultrasonography reveals similar findings in infants with PBS and PUV, including severe bilateral HUN, a dilated posterior urethra, and a large bladder that empties poorly during monitoring. Increased renal parenchymal echogenicity, cystic changes, and poor corticomedullary differentiation are signs of dysplasia [13,14]. Antenatal intervention by vesicoamniotic shunt [4,15,16] or pregnancy termination [17,18] has been considered for both conditions when severe oligohydramnios is present. Relief of urinary obstruction antenatally often fails to correct renal insufficiency [15,19]; however, pulmonary function and survival may be improved if oligohydramnios is reversed [20].

Renal dysplasia imparts a background of irreversible renal insufficiency in infants with PBS and PUV. Hyposthenuria (obligate polyuria) induced by renal tubular injury results in excessive

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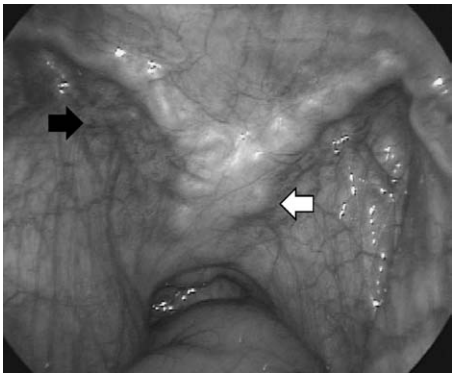

Fig. 1. Laparoscopic view of the vas deferens and ejaculatory ducts in a 6-month-old infant with PBS, showing a characteristic horizontal banding pattern of the ejaculatory ducts and absence of the seminal vesicles (*white arrow*). The site of insertion of the distended left ureter is indicated (*black arrow*).

Fig. 2. Frontal view of a 6-week-old infant with PBS, showing the characteristic lax abdominal musculature with a wrinkled appearance of the overlying skin.

clearance of free water and sodium. Severe HUN and urinary stasis increase the risk for urinary infection and urosepsis, which can incite severe dehydration and electrolyte disturbances. Preservation of renal function depends on early and effective relief of urinary obstruction and prevention of renal damage from pyelonephritis. Recognizing the severity of bladder dysfunction present is crucial to attain this goal. The incidence of renal failure continues to be 25% to 30% among children with PBS and severe PUV [21,22]. Appropriate initial evaluation and treatment for infants with PBS and PUV may help to avoid or postpone the need for renal transplantation [23], or at least improve graft survival when transplantation becomes necessary [24,25].

Prunebelly syndrome

Previously called the absent abdominal muscle syndrome [26–28] or its less offensive moniker, the triad syndrome [29], PBS [30] presents as a spectrum of involvement in the anterior abdominal wall, in the urinary tract, and in the degree of descent of the testes [31] (Fig. 2). Other serious anomalies outside the genitourinary tract are common (Fig. 3). The most severe abdominal wall defects exhibit complete absence of muscle ventral to the midaxillary line [12], which allows the entire abdominal wall to be lifted and palpated. Some infants present with more substantial or even normal abdominal wall thickness, especially in the upper quadrants [32]. The degree of abdominal wall involvement does not correlate with the severity of urinary tract impairment [31].

The ureter in PBS demonstrates gross, microscopic, and ultrastructural changes. These dilated and tortuous ureters exhibit wall thickening, which correlates with an increase in collagen deposition between muscle bundles [33]. Electron microscopy identifies massive replacement of smooth muscle architecture with fibrous and collagenous tissue, with progressive collagen deposition evident in the wider more distal ureter [34]. Clinical observation confirms that the best functioning ureter is nearest to the kidney [35]. Although ureteral dilatation is suspected to result primarily from inefficient peristalsis, distal ureteral obstruction can occur [36,37].

The bladder in PBS is vertically enlarged with an increased wall thickness but is typically not trabeculated. The dome of the bladder often exhibits a pseudodiverticulum at the urachal attachment, which may generate a patent urachus when urethral stenosis or atresia is present [38]. The trigone is broad, with the ureteral orifices displaced laterally, and vesicoureteric reflux (VUR) is detected in approximately 85% of infants with PBS [39]. The bladder outlet expands during voiding, exposing a characteristic tapered appearance on voiding cystourethrography (VCUG), even though intravesical pressures usually remain normal [40]. Inefficient bladder emptying with significant postvoid residual volumes

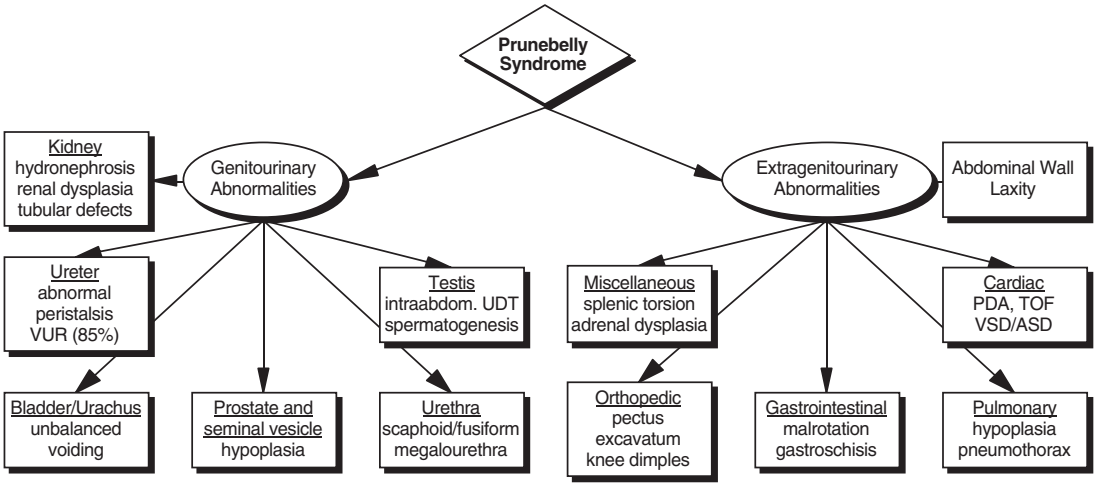

Fig. 3. Spectrum of anomalies associated with Prunebelly Syndrome (PBS). UDT, undescended testes; PDA, patent ductus arteriosus; TOF, tetralogy of Fallot; VSD, ventricular septal defect; ASD, atrial septal defect.

occurs in most children with PBS, independent of their voiding pattern (and independent of prior reduction cystoplasty) [41–43]. Although abdominoplasty improves the efficiency of bladder emptying for most children with PBS, residual volumes typically remain greater than 10% of bladder volumes [42].

Urethral obstruction from stenosis, valves, megalourethra, or atresia is recognized in as many as 25% of infants with severe renal impairment [12,44]. Stenosis can be demonstrated at autopsy as an angulation in a short segment of the prostatic urethra just above the membranous urethra [8,45,46]. This pattern, in which the membranous urethra exits from anterior wall of the prostatic urethra, can be associated with a normal or narrow caliber or with a "high takeoff" imparting relative obstruction (Fig. 4) [8]. Anterior folds of the prostatic urethral mucosa are suspected to cause obstruction when they overlap the urethral outlet (type IV valves) [8,33]. Variations on Young's type I and III urethral valves are also recognized on postmortem examination in infants with PBS [8]. Although both types of megalourethra may occur, infants with PBS account for half the reported cases of the scaphoid type [47]. The absence of tissue in all three corporal bodies (fusiform megalourethra) or merely the corpora spongiosum (scaphoid megalourethra) occurs along with urethral obstruction in a spectrum of severity, which blurs the distinction between these two types [48,49]. Fusiform megalourethra is strongly linked to severe renal impairment and neonatal demise (Fig. 5) [47]. Absence of the entire penis and urethra has been observed in infants with PBS [50].

Bilateral nonpalpable undescended testes are a characteristic feature of PBS. The testes are intra-abdominal and mobile on a long mesorchium, and both testes are typically present and viable [51]. Although the testes are generally found overlying the dilated ureters at the level of the iliac vessels, their position can span the entire course of the ureter. The vas deferens can be tortuous and thin walled with segmental atresia [52,53], and the epididymis can be detached entirely from the testis [54]. In the prepubertal period, these testes may be

Fig. 4. Voiding cystourethrogram in a neonate with PBS and a patent urachus, demonstrating an elongated and dilated prostatic urethra with a high takeoff of the membranous urethra exiting anteriorly (*white arrow*).

Fig 5. Severe fusiform megalourethra in premature infant with PBS. Note the left leg behind the megalourethra with the heel at end of the penis.

histologically indistinguishable from normal immature testes, with no difference in germ cell counts detected [55,56]. Testis biopsies may also reveal tubules lined by only Sertoli cells [57], or Leydig cell hyperplasia with hypospermatogonia [58]. Infantile PBS germinal epithelium demonstrates morphologic and histochemical similarity to embryonic germ cells and intratubular germ cell neoplasia, suggesting that a developmental arrest occurs in these testes, and that children with PBS may be at a higher risk for germ cell tumors [59].

Associated anomalies can involve the respiratory tract, gastrointestinal tract, cardiovascular system, and musculoskeletal system. Respiratory impairment results from pulmonary hypoplasia (in utero oligohydramnios) and from mechanical factors (flattened diaphragm associated with rib flaring and weakened abdominal musculature). The resultant poor expiratory effort may only become apparent clinically during postoperative recuperation [60,61]. Although a wide spectrum of rare gastrointestinal maladies have been recognized (malrotation, volvulus [62], gastroschisis [63], omphalocele [64], Hirschsprung's disease [65], and imperforate anus [39,66]), the most common manifestation is chronic constipation secondary to poor peristalsis and a generalized lack of intra-abdominal pressure [21]. Abdominoplasty and an ongoing bowel regimen are beneficial for the management of constipation [21]. Cardiovascular anomalies, most commonly septal defects (atrial and ventricular) and tetralogy of Fallot, occur in approximately 10% of infants with PBS [67]. Correction of these defects supersedes urologic reconstruction. Orthopedic abnormalities, which result from fetal compression, affect half of all infants with PBS. Common abnormalities include developmental dislocation of the hip, scoliosis, pectus excavatum, clubfeet, and muscular torticollis [68–70]. Many infants with PBS exhibit dimples on the lateral aspects of their knees without any functional orthopedic limitations (Fig. 6).

Initial evaluation

Before 1970, half of all infants with PBS died within the first 2 years of life [71]. The current prognosis and clinical management are determined primarily by the degree of renal impairment present (severe, moderate, or mild) [72,73]. When severe renal dysplasia is present, neonatal mortality generally follows acute respiratory distress owing to pulmonary hypoplasia or urosepsis [21,74]. Progression to renal failure is strongly correlated with bilateral abnormalities noted on renal ultrasonography or renography and a nadir serum creatinine level greater than 0.7 mg/dL [74]. Some infants with nearly normal urinary tracts and preserved renal function may only require surveillance, whereas others require active intervention to relieve urinary stasis and to prevent urinary infection.

Early assessment of infants with PBS is essential so that treatment can be individualized. Physical examination can reveal a palpable kidney, ureter, or bladder, suggesting that significant urinary obstruction is present. Urinalysis and urine cultures, along with assays for serum creatinine and electrolytes, can identify urinary infection or metabolic problems early enough for intervention and should be performed at regular intervals determined by their trend. Serial ultrasonography

Fig. 6. Dimple without underlying subcutaneous fat on the lateral aspect of the right knee in 6-month-old infant with PBS.

reveals the amount of renal parenchyma present and aids in the detection of progressive HUN. This preliminary investigation in the first few days of life will determine whether the infant needs only prophylactic antibiotic therapy and routine surveillance. VCUG can be postponed in infants with stable renal function to avoid introducing bacteria into a stagnant urinary system [75,76]. Infants with poor renal function, massive ureteral dilatation, a patent urachus, and high bladder residual volumes need additional investigation. VCUG will delineate urethral abnormalities, the degree of bladder distension, the extent of VUR, and the presence of urachal abnormalities. Concomitant antibiotic administration may mitigate the risk of urinary infection associated with catheterization. Nuclear renography (^{99m}TcDMSA or ^{99m}TcMAG3) aids in confirming functioning renal tissue; however, ^{99m}TcMAG3 Lasix washout renography is unreliable for the detection of obstruction in the presence of extreme ureteral dilatation and tortuosity (with or without VUR), especially in the setting of poor renal function.

Initial treatment

Specific treatment of the dilated urinary tract in PBS has remained controversial for the past 25 years. Massively dilated, poorly functioning lower ureters may predispose the infant to stasis and infection with further renal deterioration [31]. Nonetheless, more than half of children with PBS who are followed up with only minimal surgical intervention (urethrotomy for urethral obstruction) have demonstrated a satisfactory outcome with stable renal function [75,77,78]. Cutaneous vesicostomy may be beneficial when poor bladder emptying leads to urinary infection, especially if urethral stricture, valves, or atresia is detected. Although a patent urachus may initially be present in this setting, bladder drainage is unreliable, because the urachus often closes within the first several weeks of life. Urethral atresia or stenosis can also be managed successfully with progressive soft dilation of the urethra, yielding a normal caliber urethra [79].

Urinary tract decompression may be indicated when progressive azotemia occurs, especially when in utero oligohydramnios was recognized. In these cases, bilateral open nephrostomies and renal biopsies have been advocated to differentiate between renal obstruction and renal dysplasia [75]. An alternative approach advises early supravesical diversion by pyelostomy followed by total reconstruction in a single stage (bilateral tapered ureteroneocystostomy, reduction cystoplasty, bilateral orchiopexy, and abdominoplasty) [80]. Loop ureterostomy should be avoided, because it may compromise the best portion of the ureter [35,75]. Temporary end cutaneous ureterostomy may offer temporary relief of obstruction and may promote a decrease in the overall caliber of the severely dilated ureter [75], but this approach should be used with caution in infants with PBS owing to poor ureteral peristalsis and a propensity for stomal stenosis. Percutaneous nephrostomy should be reserved for infants with severe azotemia or infection requiring exigent direct renal drainage to allow survival. Although primary newborn reconstruction for PBS has been completed with excellent results [72], the use of radiographic surveillance and antibiotic prophylaxis for several months is now considered preferable to lower the risk for postoperative pulmonary complications [81]. Ureteroneocystostomy with extensive tapering is technically feasible in infants with PBS because bladder volumes tend to be substantial [31], but coincident vesicostomy or, preferably, appendicovesicostomy should be considered to minimize the risk for postoperative obstruction.

Although abdominal wall laxity may improve somewhat with age, beneficial effects from abdominoplasty are suspected to include improved respiratory and bowel function and enhanced urinary tract emptying [42]. Regrettably, increased pressure on the flattened diaphragm in these infants in the immediate postoperative period contributes to restriction of pulmonary excursion and retention of secretions. Randolph and associates recognized that the upper abdominal musculature was predictably more normal on abdominal wall electromyography; therefore, they recommended a transverse lower abdominal incision for abdominoplasty, removing the lower abdominal musculature in continuity with the peritoneum and skin [32,80]. Ehrlich and associates use a midline incision, extensive dissection of the skin, and overlapping of the anterior abdominal wall fascia along the anterior axillary lines when performing abdominoplasty [82,83]. Abdominoplasty can also be completed by the formation of two longitudinal fascial pleats that are folded medially and secured at the bases of the folds and at the midline of the abdomen [84]. This approach, espoused by Furness and associates, provides more secure suture fixation when the abdominal wall fascia is severely attenuated. A novel repair promoted by Monfort and associates

[85] using two laterally placed longitudinal incisions in the fascia, with subsequent closure in the midline, allows preservation of the umbilicus and offers excellent cosmetic results. Extensive ureteral mobilization and transabdominal orchiopexy are easily accomplished with the generous surgical exposure afforded by this technique [86].

Although transabdominal orchiopexy (without division of the spermatic vessels) can often be completed successfully in the neonate [72], achieving adequate spermatic vessel length for orchiopexy in the older infant or child with PBS may be problematic. A single-stage laparoscopic orchiopexy may be useful in select infants [87] when abdominoplasty is extraneous. A two-stage, vasal-pedicle orchiopexy [88] affords excellent success (>90%) [89], and the first stage can be completed safely using a laparoscopic approach [90].

In a comprehensive approach to reconstruction in PBS, preliminary laparoscopy is performed at approximately 6 months of age, along with a single-stage laparoscopic orchiopexy or a first-stage orchiopexy (laparoscopic division of the spermatic vessels) (Fig. 7). Ureteral dilatation, especially in infants without VUR, should be examined carefully during laparoscopy, because persistent tense distension of the distal ureter, despite the external pressure associated with pneumoperitoneum, strongly suggests distal ureteral obstruction (Fig. 8). After 2 months, the Monfort abdominoplasty with tapered ureteroneocystostomy (for persistent VUR or obstruction) and second-stage orchiopexy can be completed. The urachal diverticulum should be removed if present, but reduction cystoplasty [91] is no longer indicated. Appendicovesicostomy with an umbilical stoma facilitates intermittent catheterization to allow efficient bladder emptying and to prevent urinary infection [41]. Monitoring in an intensive care unit setting is preferable to manage the pulmonary compromise anticipated postoperatively.

Posterior urethral valves

In 1919, Young et al [92] described three distinct types of posterior urethral valves based on their cystoscopic appearance. Type I valves account for most (95%) posterior urethral obstructions, ranging from mild to severe depending on their configuration within the urethra. Abnormal insertion of the mesonephric ducts into the fetal cloaca is thought to generate obstructing fibrous stromal membranes in the place of the normal plicae colliculi [33]. Type II valves are considered artifact, resulting from muscular hypertrophy of the superficial trigone extending toward the verumontanum. The type III valve (5%) is a transverse concentric membrane distinct from the verumontanum that results from incomplete dissolution of the urogenital portion of the cloacal membrane (also found in PBS). Both types of valves (I and III) can be thick or thin, but a classic windsock appearance generally results from distension of a thin membrane. Dewan and associates [93] believe that these different types of valves actually represent varied manifestations of a congenital obstructing posterior urethral membrane.

High pressure during the storage and voiding of urine increases the workload on the distended bladder, yielding detrusor hypertrophy and an ingrowth of collagen in infant [94] and fetal [3] bladder specimens. Resultant detrusor hyperreflexia and loss of compliance promote the development of HUN, VUR, and renal damage (renal dysplasia, glomerular and tubular dysfunction). Concentration defects lead to a hyposthenuria with urine volumes large enough to impair voiding efficiency, further challenging the compliance of the ureters and bladder [95,96]. The most serious renal impairment occurs when bilateral VUR is present, forcing both kidneys to develop in a high-pressure setting [95,97]. A high risk for progression to renal failure has been recognized when renal dysplasia and bladder dysfunction exist [97]. The degree of renal dysplasia present at birth is irreversible and determines the potential for growth and function of the kidney. A nadir serum creatinine level greater than 0.8 [98] to 1.0 mg/dL [99] also suggests an impaired glomerular filtration rate (GFR) (<70 mL/min/1.73m^2) [14,100] and poor long-term renal function. Proteinuria during infancy, which indicates significant hyperfiltration, also heralds eventual renal failure [14,101].

Mitigation of urinary tract pressures during development allows amelioration of impaired kidney and bladder function. Unilateral VUR may act as a pressure vent, leading to ipsilateral (usually left-sided) dysplasia but allowing better function to develop in the contralateral kidney (VURD syndrome) [102]. Similarly, urinary extravasation (with or without ascites), a patent urachus, and a large bladder diverticulum are protective factors preserving renal function [103–107]. A spectrum of protection clearly exists; however, some children with PUV experience an importunate progression toward renal insufficiency despite these protective effects. Bilateral VUR

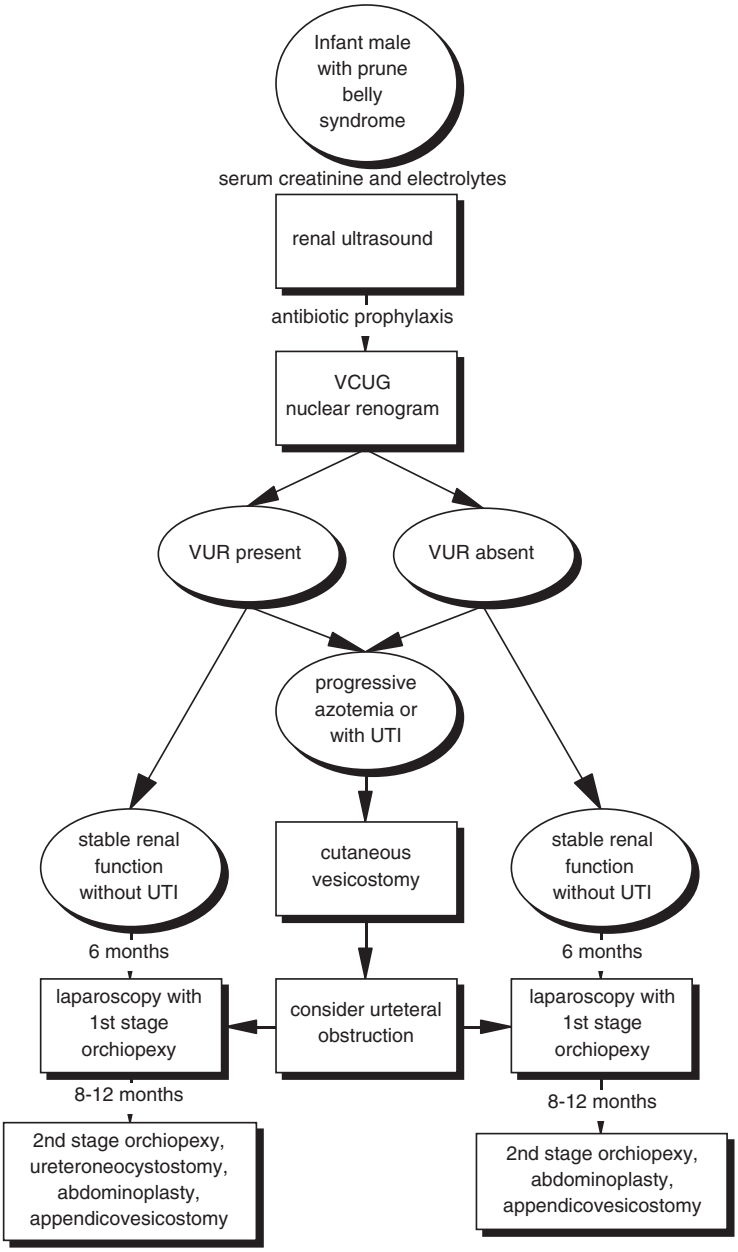

Fig. 7. Proposed management scheme for infants with PBS, incorporating laparoscopy for orchiopexy at 6 months of age, followed by definitive reconstruction 2 to 4 months later. UTI, urinary tract infection.

predisposes to worse overall renal function in comparison with unilateral VUR [95,97] (Fig. 9), but renal function also steadily declines in boys with the VURD syndrome when observed for their first decade [108].

Although any single prenatal pressure vent promotes improved bladder function, indicated by favorable postnatal urodynamic parameters (mean end-filling pressures <30 cm H_2O, and total capacity at least equal to that predicted for age), additional pressure pop-offs afford cumulative benefits [103]. Isolated antenatal urinary ascites, speculated to result from extreme bladder pressure leading to rupture, is associated with poor overall

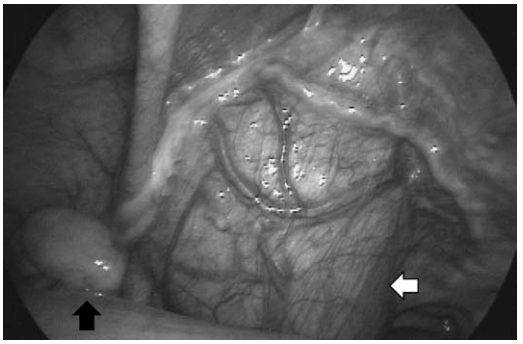

Fig. 8. Laparoscopic view in a 6-month-old infant with PBS showing a persistently distended left ureter despite pneumoperitoneum (*white arrow*), suggesting ureterovesical junction obstruction, and a high intra-abdominal left testis (*black arrow*).

renal function (mean GFR, 29 mL/min/1.73m^2). Better function follows unilateral urinoma in the absence (54 mL/min/1.73m^2) and presence (70 mL/min/1.73m^2) of ascites, with the best overall renal function occurring when bilateral urinomas appear (105 mL/min/1.73m^2) [109]. A patent urachus may be considered beneficial [103] but is most often associated with poor overall renal function [110]. The degree of bladder dysfunction without antenatal pressure pop-offs may be severe, with children exhibiting poor urodynamic characteristics (mean end-filling pressures >40 cm H_2O, and bladder capacity <75% of that predicted for age) and a greater requirement for anticholinergic therapy and bladder augmentation [103].

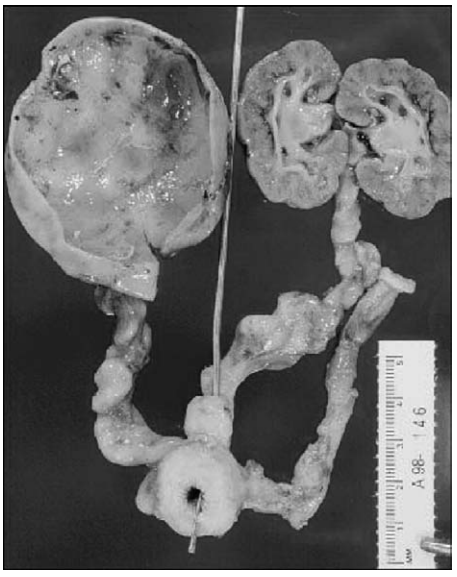

Fig. 9. Postmortem specimen from a stillborn infant with severe PUV, showing massive distension of the effaced right kidney and cystic changes in the dysplastic left kidney. The probe indicates the lumen of the markedly thickened bladder.

Initial evaluation

Currently, most infants with PUV are detected on antenatal ultrasonography. This discovery allows early postnatal treatment and clinical surveillance in a tertiary care center. Nevertheless, some infants with PUV continue to escape fetal diagnosis, because only half are detected by ultrasonography before 24 weeks' gestation [111], and the most unfortunate of these infants present clinically with acidosis, uremia, urinary retention, and urosepsis [97]. Early detection of PUV by 24 weeks' gestation identifies a high-risk group with a 50% chance of death or chronic renal failure [111]. Infants with severe PUV presenting with favorable urinary electrolytes, oligohydramnios, and fetal growth retardation before 24 weeks' gestation may undergo urinary tract decompression by vesico-amniotic shunt placement, but no long-term renal protection is usually achieved [112]. Progressive changes noted on second-trimester sonography can further delineate the postnatal prognosis. Poor postnatal outcomes (chronic renal failure or death) are predicted in 89% of infants who are found to have moderate or severe HUN (renal pelvic anteroposterior diameter ≥10 mm) and increased renal echogenicity or cystic changes, in contrast to 25% of infants lacking these ominous findings [113].

Ultrasonography performed in the neonatal intensive care unit remains fundamental to monitor the clinical progress of neonates with PUV, providing a measure of the amount of renal parenchyma and the severity of HUN. Perinephric urinoma or ascites evident on ultrasonography suggest prenatal renal or bladder rupture. Perinephric urinomas may be diffuse or localized, and the degree of hydronephrosis present may vary widely [114]. Poor corticomedullary differentiation with increased renal parenchymal echogenicity is the hallmark of renal dysplasia [13,14]. Detection of this finding bilaterally is considered a more meaningful indicator of the degree of infravesical pressure elevation than is detection of bilateral high-grade VUR [13]. HUN, urinary extravasation, and dysplasia are products of pervasive bladder pressure transmission to the upper urinary

tracts. Detection of an increased bladder wall thickness indexed to bladder filling (bladder diameter) reproducibly identifies infravesical obstruction present in children with PUV [115].

When this diagnosis is suspected in a newborn, urethral catheterization should be performed directly to allow bladder decompression until the child is able to undergo radiographic evaluation. Significant postobstructive diuresis from tubular dysfunction can ensue in cases of severe obstruction. Catheters that function poorly may actually be curled within a distended prostatic urethra, or may have entered a gaping ureteral orifice. In extreme cases, inflation of a catheter balloon may completely fill the bladder lumen and cause ureteral obstruction [116]. Radiographic confirmation of catheter position and even a prefatory VCUG can be performed in the neonatal intensive care unit using portable radiography. Voiding cystourethrosonography using echo contrast can also be used as the initial diagnostic examination to detect reproducibly the presence of PUV and VUR [117].

Fluoroscopic VCUG with views of the urethra during voiding is diagnostic for PUV. The posterior urethra is markedly dilated, and the valve appears as a thin linear defect in the column of radiocontrast. The bladder neck is narrowed and thickened, with the urinary channel displaced anteriorly. Contrast may fill the utricle, causing the appearance of a small diverticulum, or may reflux into the seminal vesicles and ejaculatory ducts. The bladder may appear diminutive because of extreme detrusor thickening when compared with the distended prostatic urethra and massively refluxing ureters (Fig. 10). VUR is usually high-grade and occurs in half the affected infants at initial VCUG, with half of these infants exhibiting unilateral involvement and half bilateral involvement [102,118]. Serial VCUG studies are useful to evaluate improvement or resolution of VUR and to confirm complete relief from obstruction following endoscopic valve incision.

Nuclear renography is essential in determining differential renal function. Use of ^{99m}TcMAG3 provides functional data along with clear visual images of the renal parenchyma and the urinary collecting system [119]. The bladder must be decompressed adequately with a catheter (gravity drainage and aspiration) to avoid overestimation of function in refluxing renal units. The combination of ^{99m}TcMAG3 renography and indirect radionuclide cystography (evaluation without urinary catheterization, before and after spontaneous micturition) aids in the detection of VUR but also provides a measure of bladder function [119]. An alternative radiotracer, ^{99m}TcDMSA, which binds to the proximal tubules and provides images of only the renal parenchyma, provides the most accurate assessment of differential renal function.

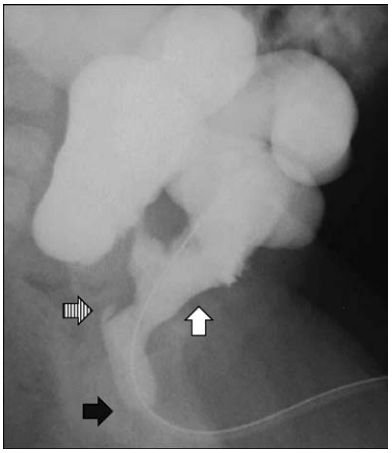

Fig. 10. Voiding cystourethrogram in a neonate with PUV and massive bilateral VUR, showing a diminutive bladder size from muscular hypertrophy (*white arrow*) and filling of the utricle (*hatched arrow*). The obstructing PUV is seen as a thin transverse linear defect in the column of radiocontrast (*black arrow*).

Initial treatment

Infants with PUV may exhibit severe respiratory distress and metabolic acidosis that requires aggressive intensive care. After the diagnosis is made and the infant is stabilized, durable relief of urinary obstruction can be achieved by endoscopic incision of the PUV. For term infants, this procedure is frequently completed under general anesthesia using an 8F infant resectoscope and a sickle blade with little risk for urethral injury. This approach has few complications, especially when compared with the high rate of urethral stricture (50%) previously reported at the site of fulguration and in the bulbar urethra while employing a 10F resectoscope and electrocautery in infants during the first year of life [120]. Selective disruption of the obstructing valves either anteriorly (1974) [121] or posteriorly (1985) [122] was formerly advocated when limitation from available endoscopic equipment was significant. Incision of the valves should be completed in the posterolateral positions (4:00 and 8:00 o'clock positions) and anteriorly (12:00 o'clock position)

to ensure complete relief from obstruction. In milder cases, fusion of the valves anteriorly may not be evident. Urethral catheter placement is rarely necessary following valve incision.

Premature or small infants may require a modified approach for the treatment of obstruction. A 7F cystoscope and a hook electrode (crafted from a 3F catheter and stylet) can be implemented for these infants, but this technique mandates extreme accuracy because it employs electrocautery and an unwieldy electrode in a diminutive space. The neodymium: yttrium-aluminum-garnet (Nd:YAG) laser can also be used to perform valve ablation [123]. Disruption of the PUV under C-arm fluoroscopic guidance may be accomplished with retrieval of a 6F Whitaker hook [124,125] or a No. 4 Fogarty balloon [126]. Although these methods offer little accuracy, excellent results following valve ablation using a 4F Fogarty balloon catheter under fluoroscopic guidance have been reported, achieving full resolution of obstruction without urethral injury in 34 of 35 (97%) infants studied [127]. Antegrade cystoscopy through the percutaneous sheath and valve incision can also be employed [128] and affords a unique perspective on the anatomy of the obstructing PUV. Urinary diversion by cutaneous vesicostomy may be prudent in select neonates, but vesicostomy cannot be proposed as an advantage over primary valve ablation when comparing mortality, preservation of renal function, or postoperative complications [129,130].

Surveillance ultrasonography performed after transurethral incision of PUV will help direct further treatment. HUN that improves after valve incision without a corresponding improvement in serum creatinine strongly suggests that significant renal dysplasia is present. These infants progress to renal failure despite urinary tract diversion. Vesicostomy should be considered when bladder emptying is incomplete despite valve incision, especially if HUN and azotemia (serum creatinine >1.8 mg/dL) are persistent. Vesicostomy has also been advocated in infants with severe bilateral VUR [129,131], because the worst overall renal function is often evident in these infants [97,132]. Ureterostomy or pyelostomy may be beneficial in atypical cases when azotemia and HUN are persistent or progressive despite efficient bladder emptying [133]. Pyelostomy or open nephrostomy provides the most certain urinary tract emptying and allows concomitant renal biopsy to be completed. This approach may be considered when the serum creatinine level fails to decrease by 10% daily to a nadir of less than 0.8 mg/dL (by day 5) [118,130] but is often the most useful when renal deterioration coexists with accumulation of perinephric urinoma or ascites after initial percutaneous drainage. High-loop cutaneous ureterostomy offers a simple and effective option for upper tract diversion [96] but also risks damage to the most normal portion of the distended ureter [134].

Despite reports supporting the concept that supravesical diversion preserves renal function in infants with severe PUV [118,135–137], it has been strongly suggested that a high incidence of renal dysplasia in this population limits any durable benefit beyond childhood [14,130,138–140]. In a group of 26 infants treated by supravesical diversion for persistent azotemia (median serum creatinine, 2.5 mg/dL), renal dysplasia was detected on biopsy in 85%. Despite diversion and a decrease in the median nadir serum creatinine at 1 year to 1.0 mg/dL, 58% of the infants subsequently progressed to renal insufficiency or failure, with 42% reaching end-stage disease at a median surveillance interval of 9 years [138]. Demonstrable ureterovesical junction obstruction was detected only rarely (4%) by antegrade pressure perfusion study performed through the supravesical diversion [138].

Most cases of unimproved HUN after valve incision are caused by severe detrusor dysfunction. An increase in bladder wall tension with high bladder filling pressures causes a functional obstruction at the ureterovesical junction and a corresponding increase in renal pelvic pressures. This valve bladder dysfunction [141] in children with thick-walled and poorly compliant bladders is accentuated by hyposthenuria and by rapid refilling of the bladder as urine in the ureters drains directly after voiding. Prolonged bladder decompression is also deleterious by disruption of normal bladder cycling, which negatively impacts bladder rehabilitation and ultimate capacity and compliance [139,140,142,143]. A critical balance exists in efforts to rehabilitate the kidneys and the bladder in children with PUV. Resolute efforts directed at preserving renal function might yield diminished bladder capacity and compliance and ultimately provoke deterioration of renal function. The Sober-en T ureterostomy has been offered as an option to preserve renal function without compromising bladder function, presupposing that ureteral peristalsis will actively fill the partially defunctionalized bladder [144].

Treatment should be designed to provide low-pressure urinary storage and complete emptying

of the bladder with voiding. Poor bladder compliance and capacity in children with severe PUV leads to more frequent bladder augmentation to achieve adequate volumes and safe storage pressures [103,139,140]. Primary valve incision tends to preserve bladder capacity and compliance and should be pursued as an initial treatment for infants with PUV. VUR resolves spontaneously in approximately 30% of infants after valve incision, indicating improved bladder pressures [122,145]; however, valve incision alone may also create a hostile situation, with excessive storage pressures when bladder volume is severely compromised. Chronically increased bladder pressure promotes progressive deterioration of renal and bladder function and favors the formation of urinary infection. Pooling of significant volumes of urine in a massively refluxing and nonfunctional collecting system (VURD syndrome) further compounds this risk.

Concern for the detrimental effects of urinary diversion may be supplanted by regard for the importance of preventing urinary infection and renal injury. Secondary vesicostomy was found to be useful in a select group of children with unrelenting sepsis despite valve ablation and aggressive medical therapy [130]. Persistent urinary infection despite vesicostomy indicates inefficient clearance of urine, most likely from a distended refluxing ureter. End-cutaneous ureterostomy of the refluxing ureter has been used in an effort to improve voiding dynamics and to aid in determination of differential renal function in these children [146]. Ureteral reimplantation of the nonfunctioning renal unit [147] has also been advocated as an alternative to nephroureterectomy [102]. Unfortunately, all of these interventions disallow bladder cycling at normal bladder pressures and disrupt rehabilitation of developing bladder function.

Use of a novel incontinent bladder pressure vent allows complete bladder emptying at safe pressures. A series of 10 infants with severe PUV and recurrent urinary infection despite vesicostomy and aggressive medical therapy have been managed at Children's Medical Center of Dallas over the last 8 years employing this principle. An incontinent ureterovesicostomy (Fig. 11) was created from the refluxing ureter in eight infants with VURD syndrome, and an incontinent appendicovesicostomy was constructed in two others. Nonfunctioning kidneys were removed by open (2) and laparoscopic (6) nephrectomy. Refluxing stomas were positioned in the diaper region. Further

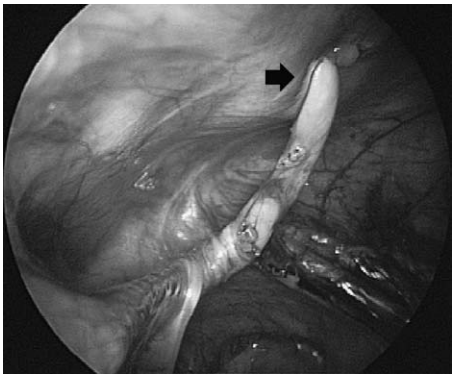

Fig. 11. Laparoscopic view of an incontinent ureterovesicostomy (bladder pressure vent) created in a 6-month-old infant with VURD syndrome and recurrent urosepsis. The ureter was brought out through the skin at the lower port site (*black arrow*) during laparoscopic right nephrectomy.

urinary infection was subsequently prevented in all infants. Urodynamic evaluation indicated normalization of bladder capacity and compliance over the subsequent 3-year interval in all but one child. In that case, the refluxing pressure vent was removed after only 1 year, and progressive deterioration of bladder compliance ensued. Augmentation cystoplasty was ultimately required owing to recurrent urinary infection and marked HUN.

Videourodynamic evaluations revealed ureteral leak pressures ranging from 15 to 20 cm H_2O and filling of the pressure vent to the level of the rectus fascia before urinary leakage. Appendicovesicostomy channels reached a higher pressure of 30 cm H_2O before venting occurred. These results suggest that an enhanced level of intrinsic luminal resistance is provided by using appendix versus the ureter, reminiscent of the urodynamic findings reported in continent Mitrofanoff conduits in children, also comparing the appendix and ureter [148]. Urinary continence and a normal voiding pattern were achieved in five boys after bladder venting was eliminated by ureteral reimplantation (2) and endoscopic injection therapy (3). One boy with severe developmental delays and three with less than 3 years' surveillance continue bladder cycling with their pressure vents intact. The remaining boy is continent with intermittent catheterization following augmentation cystoplasty.

These findings suggest that the most effective use of the refluxing ureter in the VURD syndrome may be for bladder rehabilitation rather than

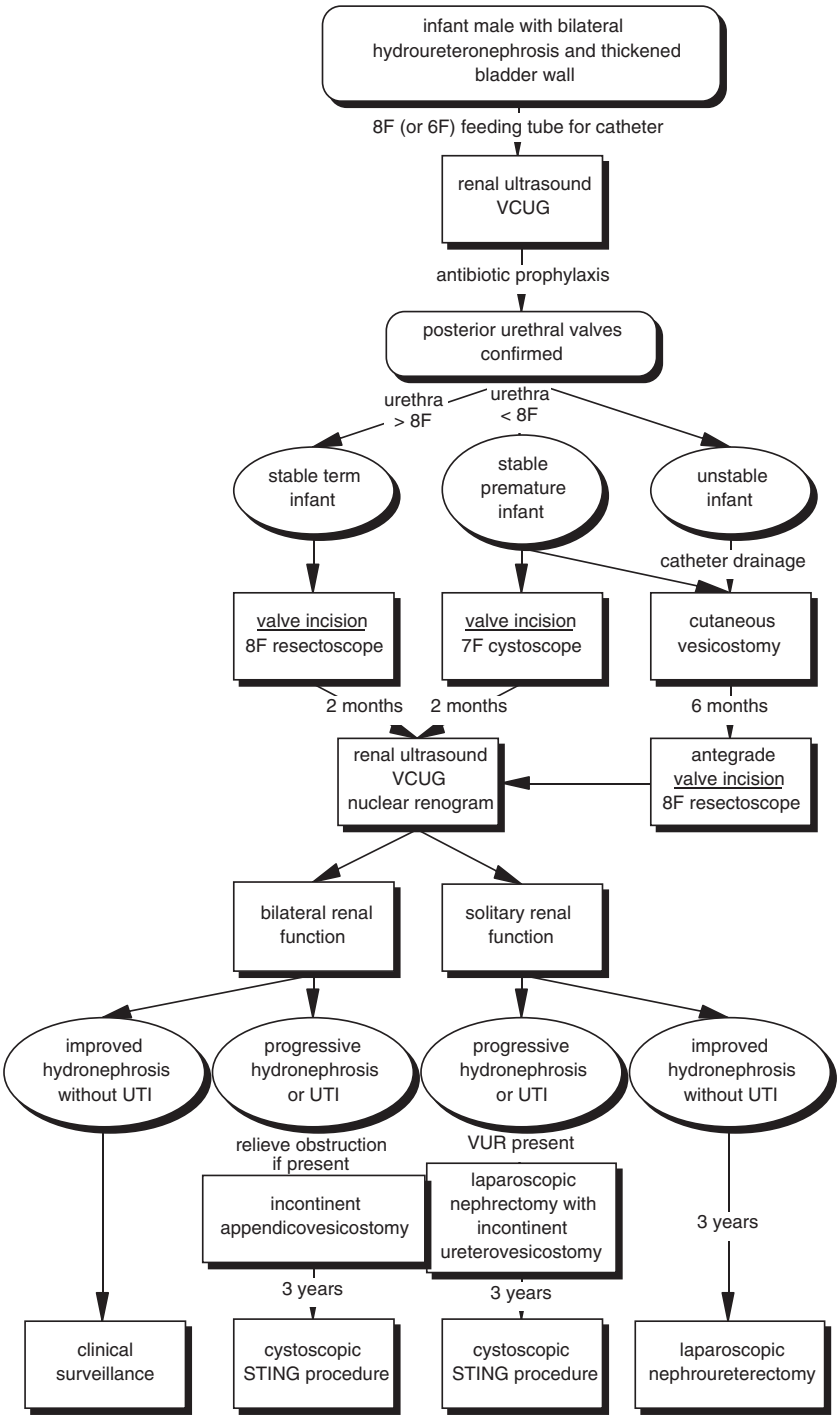

Fig. 12. Proposed management scheme for infants with PUV incorporating the use of a temporary incontinent bladder pressure vent to aid in bladder rehabilitation when progressive hydronephrosis or recurrent urosepsis is present. UTI, urinary tract infection.

bladder augmentation. Use of the appendix as an incontinent pressure vent may be even more beneficial by allowing a higher bladder storage pressure to enhance the effectiveness of bladder cycling and rehabilitation. These pressure vents, which are considered to act as temporary "training wheels" for the bladder allowing effective bladder cycling at safe pressures, may be incorporated into the management scheme for infants with severe PUV (Fig. 12).

Summary

A comprehensive approach must be pursued when treating infants with PBS and severe PUV to preserve renal and bladder function. Because the degree of renal dysplasia present is determined antenatally and is not reversible, preservation of renal function requires optimal bladder rehabilitation and prevention of urinary infection. Infants with PBS and PUV demonstrate impaired voiding proficiency. Those with PBS exhibit myogenic failure with incomplete emptying. Ensuring effective bladder emptying is crucial and can be aided by incorporating an appendicovesicostomy in reconstruction for infants with PBS. Infants with severe PUV typically possess small capacity bladders with poor compliance, which also promotes progressive renal deterioration. Rehabilitation of bladder function can be achieved by creating an incontinent bladder pressure vent allowing effective bladder cycling at safe pressures. This approach is especially appealing in the setting of recurrent urosepsis.

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Initial management of complex urological disorders: bladder exstrophy

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Children born with *bladder exstrophy* have a considerable challenge. With careful planning and an appropriate team, however, many of these boys and girls can lead a normal life. Many leaders in society born with bladder exstrophy are a testimonial to this, and seem to have viewed their initial handicap as a stimulus for a productive life. The initial medical management of these children therefore involves not only providing the basic supportive measures and operative treatment, but also providing information, support, and encouragement to their families.

Incidence and inheritance

Bladder exstrophy is uncommon, reported once in every 20,000 to 40,000 live births [1]. In a multicenter retrospective study, pooled worldwide data of nearly 6.3 million births between 1970 and 1975 placed the prevalence at 3.3 per 100,000 births (1 in 30,000) [2]. Although the lesion is rare, some families are at higher risk. Of 2500 index cases from another survey [3], nine affected siblings were found. This represents an overall risk of a second affected family member of 3.6%. Of 215 children born to parents in this group with exstrophy or epispadias, three children inherited bladder exstrophy (1 in 70 live births, or 1.4%). The risk of two affected siblings is about 1% [4].

Although most patients with classic bladder exstrophy have few associated defects, exstrophy associated with exomphthalmosa has been recorded in successive pregnancies [5]. In addition, two patients with bladder exstrophy have developed Wilms' tumor, an unlikely event considering the relative incidence of the two conditions. Despite occasional clustering of individuals with the defect, little is known about risk factors for bladder exstrophy. In one study, women less than 20 years of age and high parity (3+) had increased risk for children with exstrophy [2]. Maternal use of progestins also has been implicated [6]. Despite these occasional reports, most cases are not associated with any particular risk factor.

The male-to-female ratio for classic bladder exstrophy is between 1.5:1 and 2:1 [2,7]. The ratio generally is higher for complete epispadias, with reports of male predominance as high as 3.5:1.

Embryology and pathophysiology of exstrophy

Before 2 weeks' gestation, the cloacal membrane occupies a prominent position on the infraumbilical abdominal wall. Mesenchyme from the primitive streak migrates between the ectoderm and endoderm of the cloacal membrane to reinforce the infraumbilical area while the cloacal membrane regresses. Before rupture of the cloacal membrane, the urorectal fold joins the membrane to separate the cloaca into the urogenital and anal components. Rupture of the membrane at the base of the genital tubercle establishes the urogenital opening [8].

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There are several theories to explain the abnormal anatomy in exstrophy. Patton and Barry [8] suggest abnormal development of the genital hillocks with fusion in the midline below rather than above the cloacal membrane. This abnormal cephalad migration of the cloaca would result in instability and premature rupture of the cloaca before mesodermal ingrowth occurs. Observations on the relative frequencies of the various exstrophy variants suggest that if the exstrophy results from abnormal caudal displacement of the genital tubercle, the defects associated with minimal displacement (epispadias) should be more common than those associated with further displacement (classic bladder exstrophy), but this is not the case.

In 1962, Marshall and Muecke [9] theorized that the normal mesenchymal migration between the leaflets of the cloacal membrane in exstrophy is truncated, owing to increased thickness of the membrane. Rupture of the membrane after completion of the caudal growth of the urorectal septum, without reinforcement of the mesodermal layer, would result in bladder exstrophy. This idea is supported by Muecke's experiments in chick embryos. At 48 to 52 hours of gestation, a smaller triangular piece of Millipore plastic was placed at the region of the cloacal membrane. Several chicks developed the characteristic appearance of exstrophy, probably because the plastic prevented mesodermal migration at this crucial stage of development. In a similar set of experiments, Thomalla and Mitchell [10] found that laser trauma to the cloacal membrane as late as 61 hours (before curling of the tail bud) results in exstrophy in chicks.

A more recent report based on observations of normal development in rat embryos may refine Muecke's theory further. Early in rat development, marked cranial movement of the yolk sac separates it from the cloacal membrane. In the region between the yolk sac and the membrane, the genital tubercle proliferates and forces the cloaca into a dorsal caudal position. A thick plate of mesenchymal tissue lies at the base of the genital tubercle. Failure of the cranial progression of the yolk sac in exstrophy would prevent migration of the genital tubercle and posterior displacement of the cloaca. The abdominal wall muscle and genital hillocks (labioscrotal or genital folds) then would fail to meet at the midline. The subsequent superficial cloacal membrane, poorly reinforced with mesoderm, would be prone to rupture, resulting in exstrophy. This theory, which refines rather than refutes the chick embryo results, may explain the shortened umbilical-anal distance seen in nearly all patients with exstrophy or epispadias, as well as the clinical appearance of several of the exstrophy variants [11].

Clinical presentation

Early descriptions of bladder exstrophy in newborns were made in 1747 by Mowat [12], in 1901 by Connell [13], and by Hall in 1953 [14]. No attempt was made to correct the defect surgically in these early reports. Initial attempts to control urine soiling and pain resulted in devices designed to collect the urine and protect the exposed bladder from contact with clothing.

Today, prenatal ultrasounds may suggest bladder exstrophy in a fetus, but the diagnosis is not made consistently before birth because of a lack of prenatal studies or a false-negative antenatal ultrasound. The sonographic absence of a normal bladder in association with an anterior abdominal mass and low-set umbilicus are prenatal findings suggesting bladder exstrophy, but other abnormalities such as omphalocele and gastroschisis also have this appearance [15]. Ultrasonographers can characterize these changes as early as the twentieth week of gestation [16–20].

Anatomy

Children with bladder exstrophy have few defects besides the exposed bladder (Fig. 1). The associated abnormalities are confined to the development of the abdomen and perineum, the urinary tract, the genitalia, the spine, and the bony pelvis.

The diamond-shaped area bounded by the umbilicus, the anus, the rectus abdominis muscles, and the skin overlying the puborectal sling houses the defect most apparent in children born with exstrophy. The umbilical-anal distance is short because the umbilicus is placed more caudally than normal and the anus is anterior. The area between the displaced muscles and the margin of the exposed bladder is covered with shiny fibrous tissue. The rectus muscle inserts normally at the pubic tubercle. The displaced pubic bones carry the rectus muscles to a lateral position. This displacement of the rectus muscles widens the internal inguinal canal and places the internal inguinal ring just beneath the external inguinal ring. For this reason, indirect inguinal hernia and incarceration are common, particularly in boys [21–24]. Because the bladder is not located

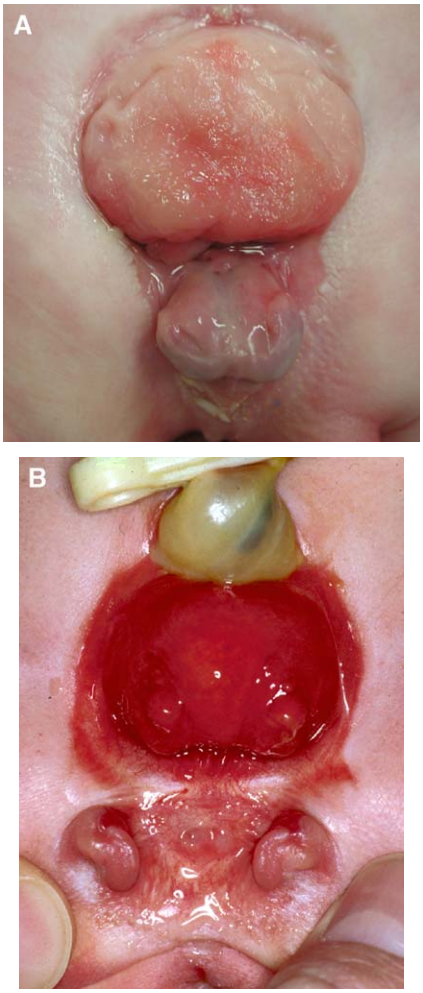

Fig. 1. (*A*) Bladder exstrophy in 6-week-old boy prior to complete closure. His parents covered his bladder with plastic wrap placed in the diaper. Note absence of polyps on the urothelium despite 6 weeks of care at home. (*B*) Bladder exstrophy in a newborn girl.

initially in the pelvis, the peritoneal reflection is deep before reconstruction, and a disproportionate percentage of peritoneal contents are located posterior to the bladder at birth.

The bladder size varies from a small patch to a larger prolapsing body of 15- to 30-mL capacity. The bladder urothelium appears normal at delivery, but can develop a polypoid appearance with exposure to the environment. Direct contact with diapers or clothing increases the inflammatory response and worsens the polypoid change. Microscopic changes in the transitional epithelium are present shortly after birth [25]. In untreated patients, these changes result eventually in squamous [26] or adenomatous [27] metaplasia, which later proceeds to squamous cell carcinoma or adenocarcinoma in patients who live longer [28,29]. Because the bladder has normal blood supply and normal neuromuscular activity, it should function normally once it is closed [30]. At least two studies, however, have suggested poor detrusor function after successful closures [31,32].

Rectal prolapse may develop as long as the bladder is exposed. The authors know of no cases in which this has occurred in a patient with a closed bladder. Poor support of the displaced anal sling mechanism, along with the Valsalva effect of crying in these children, results in rectal prolapse. Although no specific surgical treatment is necessary for rectal prolapse other than to close the bladder, some advocate fixing the rectal wall to the sacrum at the time of closure to prevent recurrent prolapse of the rectum.

Few renal anomalies occur in patients with bladder exstrophy or epispadias. Duplication of the ureter may occur and must be recognized before closure to avoid injury to one of the ureters. The authors have observed a boy born with a multicystic dysplastic kidney, but they do not believe this is related to the primary bladder defect. A few patients have developed hydronephrosis when the bladder remained exposed for long periods, presumably because of thickening of the wall of the uncovered bladder. This problem is not seen in infancy. Because of the deepened peritoneal cul-de-sac beneath the bladder, particularly in exstrophy, but also to a lesser extent in complete epispadias, the ureters course deeply through the bony pelvis to emerge through the bladder muscle with almost no submucosal tunnel. The result is vesicoureteral reflux in nearly all patients who have undergone bladder closure [32]. Ureteral peristalsis is normal [33]. A few patients have had spontaneous resolution of vesicoureteral reflux following bladder closure, but this is the exception.

The penis in boys with bladder exstrophy is short and wide because of separation of the pubic bones, which prevents the corpora cavernosa from joining in the midline at the usual position near the base of the pubis. As well, the deep corporal bodies are shortened, as measured by cavernosography [34]. Marked dorsal chordee is present with a shortened urethral plate. The superficial neurovascular bundles are displaced laterally. The pudendal nerves innervating the corpora in these patients emerge from the sacral trunk (S2 through S4) and pass posterior to the pelvic floor muscles, medially

to the ischial spines, and into Alcock's canal [35]. A duplicate urethra has been reported [36], which may be incorporated into the epispadias repair [37]. The corpora are nearly always sufficient for reconstruction. Gender reversal in classical bladder exstrophy is never necessary. Sexual function is usually adequate in boys with exstrophy despite the shortened penis and chordee [38].

Following reconstruction, men with bladder exstrophy have fathered children, but fertility rates are decreased [39]. A tenfold higher than normal incidence of cryptorchidism has been reported in patients with exstrophy or epispadias [23]. In the authors' experience, however, despite testes that appear to be in the inguinal canal at initial examination, most can be manipulated into the scrotum without difficulty following bladder closure. Before initial bladder closure, the epididymis [40], vas deferens, ejaculatory ducts, and seminal vesicles are normal. This suggests that the undescended testis noted in bladder exstrophy is primarily anatomic (or mechanical) and not an endocrine problem.

Because of a lack of a shutter mechanism in the inguinal canal, boys and girls with bladder exstrophy have an increased risk for incarcerated hernia. In one study, 56% of boys and 15% of girls developed inguinal hernias over a follow-up period of 10 years; 46% of the boys presented with incarceration requiring emergent management [23]. Another retrospective review of 70 consecutive patients with bladder exstrophy noted that 42 (86%) boys and three (15%) girls developed inguinal hernias, bilateral in 78% of the cases. No recurrence following correction occurred in females, whereas 17% of boys developed a recurrence [24].

Females with bladder exstrophy have a hemiclitoris on each side. The vaginal orifice may be duplicated, and is located just inferior to the distal extent of the exposed urethra. The vaginal orifice is usually narrow and displaced anteriorly [41]. The vagina and uterus may be duplicated. The ovaries and fallopian tubes are usually normal. As in males, the severity of the genital defect varies. Vaginal and uterine prolapse occur at an earlier age in women with bladder exstrophy. Most women born with bladder exstrophy report normal sexual desire and have delivered normal children [42]. Caesarean sections are often suggested to decrease the incidence of prolapse following delivery [43].

In nearly all cases, patients with exstrophy or epispadias have some degree of pubic diastasis. Pelvic growth in length and width is normal [44,45]. The hips are rotated outward. Despite the rotation, few hip or gait problems result, particularly if closure is performed at an early age. Many patients have a waddling gait in early childhood, which becomes less evident later. Congenital hip dislocation has been reported in two cases [46]. Unlike patients with cloacal exstrophy, patients with classic bladder exstrophy have few spinal defects [47].

Initial management

Babies born with bladder exstrophy have no life-threatening complications related to the bladder defect. Transfer to an "exstrophy center" should be considered shortly after birth, however, primarily to counsel the family and introduce them to the team of physicians who will be involved in the long-term care of their child. The exstrophy team is led by the pediatric urologist, and includes the pediatric anesthesiologist, the pediatric orthopedic surgeon, the neonatologist, and the pediatric urology and general pediatric nurses [48]. When transfer requires significant travel, the patient initially is hydrated adequately at the referring hospital. Saran wrap should be placed over the exstrophied bladder to prevent trauma to the urothelium. Gauze or petroleum jelly is not used because this dressing tends to dry and denude the epithelium.

Upon arrival at the center, the family meets the members of the exstrophy surgical and support teams. Although children with classic bladder exstrophy have few renal problems, a renal ultrasound is performed to identify hydronephrosis or duplex kidneys. Reports of older exstrophy patients developing latex allergies have identified the need to prevent exposure to the latex antigen. Children with exstrophy are treated in a latex-free environment throughout the hospital stay and at home. Generally, babies feed well and do not have any other medical conditions preventing them from going home soon after birth.

Although parents generally are anxious and want their child "fixed" as soon as possible, the authors aim to schedule the exstrophy repair on a day when all specialists in the team are available. For a procedure that requires a tremendous attention to detail, it is important to optimize operating conditions. The child's family is nearly always concerned about trauma to the bladder mucosa. Instructions are given on bladder management (saran wrap dressing) and parents are sent home

before the operative date. This allows the infant and mother to bond before the complicated surgical repair. The authors have found that when the children return for surgery, the bladder mucosa looks healthy, even up to 6 weeks after delivery.

History of surgical management

Various surgeons can be credited with the major advances in bladder exstrophy repair. Robert D. Jeffs began his career at the Hospital for Sick Children in Toronto and moved to the Johns Hopkins Hospital in 1975. For 20 years he refined the understanding of exstrophy by specializing his interest in this difficult anomaly. John P. Gearhart has carried on Jeffs's work and continues to nurture the largest single institution experience. Michael E. Mitchell, in Seattle, resurrected the single-stage complete exstrophy closure that incorporates epispadias repair with bladder closure. Innovative surgery and refinement based on large clinical experiences have improved continence rates following staged or single-stage exstrophy closure at these two centers, respectively. A brief retrospective of previous approaches to this difficult problem provides perspective on how much progress has been made over the last half century.

In 1850, diversion of urine to the colon in a patient with bladder exstrophy was accomplished by creating a crude anastomosis between the bladder and sigmoid colon. At least one patient treated in this way managed to divert the urine to the rectum by wearing a pad that closed the abdominal opening. By 1853, Richard attempted closure of the bladder, but the patient died of peritonitis [49]. Pancoast performed another unsuccessful closure in Philadelphia in 1858 at the Clinic of the Jefferson College (The Gross Clinic). Shortly after, Ayres managed a successful closure in a 28-year-old woman who reported marked improvement in pain from the irritated exposed urothelium [50].

By the beginning of the twentieth century, more modern techniques were used to attempt continent reconstruction. To better approximate the pubic bones, Trendelenburg first attempted sacroiliac osteotomy in 1892. The first patient became anemic and died. Trendelenburg [51] then used innominate osteotomy to close three additional patients, one boy and two men, in 1906. Although transient control was achieved in the boy, neither of the men improved after the procedure. Few attempts were made to close the bladder during the next 30 to 40 years. Instead, most patients underwent ureterosigmoidostomy combined with cystectomy [52]. In 1922, Young reported a successful bladder closure in one female patient. The bladder neck later was rolled into a tube to provide continence. The patient developed a dry interval of 3 hours. Despite Young's success in this patient, most surgeons continued to use cystectomy and urinary diversion until the 1950s [22,53].

Over the past 50 years, the focus has shifted away from urinary diversion to preservation of the bladder. In 1958, Schultz [54] revisited Trendelenburg's idea of rotating the innominate bones to reduce the pubic diastasis. He reported the use of a bilateral iliac osteotomy, followed 2 weeks later by bladder closure and approximation of the pubic symphysis in a female. The patient reportedly became continent within a week of removing the bladder catheter and remained so. Schultz believed that closer apposition of the pubic bones would better re-create the normal anatomy of the pelvic musculature. Better function of the urogenital diaphragm seemed to provide urinary continence in this patient. Schultz's initial success led to a strong advocacy for osteotomy. Lattimer and Smith [55] (1966) and Chisholm [56] (1962) each reported a large series of patients using osteotomy at the time of bladder closure, which was done with bladder-neck tightening to provide continence.

Unfortunately, despite a few early successes, urinary continence has been difficult to achieve for most. Renal deterioration was common. Modification of Young's continence procedure [57] by Dees [58] to incorporate the prostatic urethra and bladder neck in the rolled urethral strip improved urinary control. Later, Leadbetter [59] reimplanted the ureters, moving them cephalad to allow the trigone to be incorporated into the tube to lengthen the bladder neckplasty further. Although these modifications resulted in suitable dry intervals for some patients with complete epispadias, continence in exstrophy patients remained discouraging [60,61].

Jeffs [62,63] and Cendron [64,65] noticed the protection that a wide, open bladder neck provided in the incontinent epispadias patient. They separately proposed a staged approach, first converting exstrophy to incontinent epispadias with an initial bladder closure but no bladder neck reconstruction (BNR). BNR was postponed until years later. This revolutionized exstrophy management and is still a viable option offered by many centers today. Ansell [66,67] observed that

the more mobile infant pelvis made apposition of the pubic bones easier and helped to achieve a better abdominal closure. The staged approach often is performed within the first 48 hours of life, and therefore many surgeons do not include the osteotomies as a standard part of the procedure.

One giant step in dealing with exstrophy closure was developed individually by both Kelley [68] and Mitchell [69] over the past 10 years. Their approaches include attempts for early continence to encourage the bladder to empty and fill in infancy. In the Mitchell technique, this includes a complete disassembly that in boys separates the penis into its three components, the two erectile bodies and the corpora spongiosa, including splitting the distal glans. This repair has allowed the "hernia" of the epispadiac plate, including bladder and urethra, to be closed and placed deep within the pelvis in its normal anatomic position. Early results suggest that this will improve continence and produce more consistent success for children with bladder exstrophy. The authors' experience is consistent with these results.

Current surgical management

Modern techniques in exstrophy reconstruction attempt to provide adequate storage and urinary continence while preserving renal function. Even patients with a small bladder may develop surprisingly good bladder growth following successful primary bladder closure and epispadias repair [70]. In boys, penile reconstruction provides an erection straight enough for vaginal penetration and a urethra that allows for upright voiding with laminar flow voiding. Obviously, a good cosmetic appearance is essential in both sexes. Two types of repairs are performed in exstrophy centers, the staged repair and complete primary repair.

Staged repair

The staged repair begins with closure of the bladder shortly after birth with or without bilateral posterior iliac or anterior innominate osteotomy. The bladder closure is followed by an incontinent period during which the bladder gradually enlarges. Epispadias repair in boys is performed during the incontinent period—usually between 12 and 18 months. No attempt is made to provide continence until 3.5 to 5 years of age, when bladder neck plasty is considered. At that time, bladder volume is assessed. BNR is not attempted until an adequate bladder capacity is obtained. In most cases, a 50- to 60-mL capacity is adequate [71]. Even when the bladder reaches adequate size, the child also must be well motivated to be dry before BNR should be undertaken. Improved genital reconstruction techniques have resulted in better cosmetic appearance and sexual function, especially in boys.

Complete primary repair (Seattle)

The authors use a modification of the complete primary repair described by Mitchell (Fig. 2). The authors begin all exstrophy closures as the first and only case of the day, which is rarely possible within 48 hours of the patient's birth. The authors assemble the surgical team and endeavor to perform the complete disassembly within the first few weeks of life. If care is taken to prevent bladder trauma, the authors have been pleased with the bladder appearance and function when the closure has been performed as late as 6 weeks of age. When appropriate, an epidural catheter is placed before beginning the procedure. The child is prepped, allowing for the entire lower half of the thorax, the entire abdomen pelvis, and lower extremities to be exposed surgically. The orthopedic surgeons begin the procedure by performing bilateral anterior iliac osteotomies in all patients. The authors believe that osteotomies are beneficial even in young infants and those with minor degrees of exstrophy.

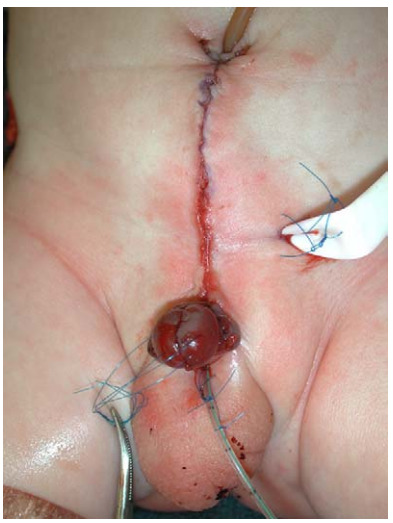

Fig. 2. Postoperative appearance in the boy in Fig. 1 following complete closure. Urethra is left as a penoscrotal hypospadias and will be corrected at 6 months with a hypospadias repair.

Once the osteotomy is completed, the exstrophy closure is begun. Umbilical artery catheters are placed in the ureteral orifices and the bladder and penile-shaft skin are circumscribed. Dissection continues to mobilize the bladder and skin surrounding the penis. The corporal bodies are defined and separation is begun to help identify the boundaries of the urethral plate. The umbilicus often is preserved but moved cranially to the normal anatomic position at the level of the anterior-superior iliac spines. The bladder dissection is performed deeply into the pelvis down to the urogenital diaphragm. In the authors' center, a muscle stimulator is used to identify the deep pelvic muscles and to define the levator complex and urogenital diaphragm, helping define the lower limit of the dissection and to position accurately the bladder neck and proximal urethra.

The dissection is begun on the ventral surface of the penis approximately midway along the penile shaft at the junction between the corpus spongiosa and the corporal bodies. At this position, the spongiosal component is separated more easily from the corpora. The dissection is continued distally to the glans, which is split on the midline. The proximal spongiosal tissue is then dissected further proximally to and beyond the level of the prostatic urethra and finally to the bladder neck.

The bladder neck is released from the levator complex and the dissection is carried deeply to the level of the perineal neurovascular bundle, which is preserved carefully. The authors' experience has been that the bladder, bladder neck, and proximal urethra can be brought to a dependent position deep within the levator sling. Positioning the bladder-neck continence mechanism within the pelvic floor musculature is essential to subsequent development of continence and volitional voiding.

Once the bladder and urethral plate are mobilized adequately to allow deep pelvic placement, the closure is begun using interrupted 5-0 Polyglactin or Polyglyconate sutures for the bladder and 6-0 and 7-0 sutures for the urethra. The ureteral catheters are brought out the urethra and a suprapubic catheter is placed through the umbilicus. A sheet of Alloderm (acellular dermal graft, Life Cell Corporation, Branchburg, New Jersey) is placed over the suture line with the membrane side up. This sheet is secured with interrupted sutures in a quilting fashion. If required, the umbilicus is reconstructed. Various types of umbilicoplasties have been described [72,73]; the authors prefer creation of a circular flap surrounding the suprapubic tube.

The penile reassembly is performed, placing the urethra ventrally and carefully placing interrupted sutures in the tunica to reapproximate the corpora. It is important to prevent tension on these sutures to preserve blood flow and prevent penile ischemia with resultant damage to either glans. The authors believe that osteotomy minimizes tension on the perineal neurovascular bundle that reduces risk for distal corporeal or glanular ischemia following the reconstruction. Finally, interrupted horizontal mattress 0 Polydioxanone sutures are placed in the pubic symphisis, allowing for the knot to be secured on top of the pelvic closure rather than in opposition to the bladder neck on the undersurface of the pubic bones. These sutures are tied down while reapproximating the pelvic bones. A latex-free Penrose drain is placed through a separate stab incision; the fascia is closed with interrupted sutures, and the skin is closed with subcuticular sutures. The osteotomy incisons are closed and the tubes secured with interrupted nylon holding sutures.

Although a hernia rarely is observed before bladder closure, the authors recommend bilateral herniorrhaphy at bladder closure to prevent incarcerated hernia, which is more common after closure than before. A properitoneal approach through the abdominal incision obviates an additional inguinal incision [23]. In many cases, however, the authors make a small inguinal incision on each side. Orchiopexy is performed later if the testes are truly cryptorchid. Usually, however, the testes only appear high because of the laterally displaced rectus muscle.

The child then is placed in a full-size stretcher with orthopedic traction bar (Fig. 3). Although there are many techniques for pelvic immobilization, including a "mermaid dressing," the authors have tended to use modified Bryant's traction in infants and an external fixator in older children. The authors strongly believe that immobilization with traction rather than a wrap results in greater pelvic stability and improved ability to evaluate the child's wounds postoperatively. This traction is maintained for approximately 3 to 4 weeks, although the authors have begun to consider making timing decisions based on bony changes on pelvic radiograph.

Postoperative care

The child remains in hospital as long as traction is needed. Antibiotic prophylaxis is begun and is continued at home because of the high

Fig. 3. Fixed traction in the newborn following complete repair.

incidence of vesicoureteral reflux. The Penrose drain is pulled back as drainage decreases and removed once it has stopped. At 2 weeks, a cystogram and stentograms are performed; if there is adequate drainage around the tubes with no exstravasation, the stents are removed. The suprapubic tube is clamped and postvoid residuals are performed to determine whether bladder emptying is occurring. The child is sent home with suprapubic tube in place with daytime clamping and overnight drainage. The child's parents are taught how to measure postvoid residuals. A return visit and cystogram is scheduled for 1 to 2 weeks postdischarge and the suprapubic is removed if there is adequate emptying. Regular ultrasounds are performed to monitor the upper tracts. If the urethra has not been brought successfully to the urethral meatus and a penoscrotal hypospadias has been constructed at the completion of the reassembly, the hypospadias repair is performed at 6 to 9 months of age. Children who develop recurrent infections with upper tract changes may require reimplant surgery.

This approach to bladder exstrophy repair has resulted in infants who seem to store and void rather than continuously leak urine. The ability to assess future continence will be crucial as these children reach potty-training age. Adequate cosmesis with no damage to the corpora or glans is critical in this single-stage repair. Early reports of penile injury need to be assessed carefully [74]. With adequate osteotomies and traction, the authors believe the rate of dehiscence and corporal/glanular injury should be low. It is hoped that with improving techniques, children with bladder exstrophy will void well with adequate bladder volume and muscular control to be continent.

Summary

Bladder exstrophy is a rare condition associated with lifelong issues, including infection, renal insufficiency, incontinence, and fertility. Despite the seriousness of the defect, many children do well long-term and lead normal lives. This outcome is possible with a team of physicians well versed in the management and care of these children. With new operative techniques, children require fewer surgeries and have more hope for continence. With close follow-up, no child should develop renal insufficiency. Families should be reassured that a normal life and parenthood with normal sexual function are possible.

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Initial urologic management of myelomeningocele

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Myelomeningocele (MM) affects as many as 1 in 1000 births, comprising the most common cause of pediatric neurogenic bladder and paralysis. Since the advent of the ventriculoperitoneal shunt, morbidity from the condition usually arises from the Chiari malformation, urologic complications, and orthopedic disabilities. Accordingly, children born with MM preferably are evaluated and managed by an interdisciplinary team including pediatric urologists, neurosurgeons, and orthopedists and developmental pediatricians, as well as specialized nurses, physical therapists, dieticians, and social workers. Together these professionals must interact with the patient and family from the time of diagnosis throughout childhood to develop plans for the management of medical and social issues arising from this condition. Despite great advances in caring for patients with MM, there remains a need for evidence-based outcome studies to define optimal management. The authors' experience derives from an interdisciplinary team program centered at the Texas Scottish Rite Hospital for Children, which maintains an active census of over 800 patients with MM.

Disordered innervation of the detrusor musculature and external sphincter in patients with MM adversely affects bladder function and potentially threatens the upper urinary tracts. In recent years, it has become clear that children with this condition can be categorized into high- and low-risk groups for secondary damage from a neurogenic bladder based on intravesical pressure. Those with elevated pressure are at risk for hydronephrosis or reflux, and there is evidence suggesting that early management of high pressure protects the bladder from additional damage, reducing the need for augmentation. Management decisions made during infancy potentially impact long-term outcomes for preserving renal function and achieving urinary continence. This discussion focuses on the initial urologic care of infants with MM, emphasizing the controversy regarding urodynamic versus radiologic-based management of a neurogenic bladder.

Prenatal issues

Increasingly, the diagnosis of MM is made prenatally based on an elevated alpha fetoprotein blood level detected by amniocentesis or fetal sonography demonstrating the spinal cord defect. This early diagnosis subsequently has led to interest in in utero surgical correction. Currently, a National Institutes of Health sponsored multicenter randomized trial is seeking to determine the safety and benefits of this approach compared with standard neurosurgical repair in the newborn period. Reports prior to this project are descriptive and with mixed outcomes. The severity of the Chiari malformation may be diminished by prenatal intervention, but no obvious improvement in bladder function has yet been noted.

Initial postnatal management

The initial urologic care of newborns with MM is rarely emergent. Often, consultation is not requested until after neurosurgical closure of the spinal cord defect. All of these infants must be assumed to have a neurogenic bladder, because

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only 5% of MM patients can void spontaneously by the typical age of toilet training. Nevertheless, the specific abnormalities vary considerably and are not predicted by the level of the spinal cord defect or the neurologic examination. Furthermore, bladder dynamics are temporarily affected by spinal cord surgery, which often results in areflexia with urinary retention. Many patients initially require intermittent catheterization, which should be performed at sufficiently frequent intervals to avoid bladder overdistention. Spontaneous voiding usually resumes within a few days, but some patients still need intermittent catheterization when discharged home.

Baseline urologic investigations include renal/bladder sonography and a voiding cystourethrogram (VCUG), which may already demonstrate evidence of neurogenic bladder dysfunction. Hydronephrosis is found in 7% to 30% of infants [1,2], although sometimes this upper tract dilation only reflects temporary urinary retention; reflux occurs in approximately 20% of infants [1]. Infants with hydronephrosis or reflux are started on antibiotic prophylaxis pending further evaluation. All urologic interventions, including intermittent catheterization, radiologic procedures, and surgeries in children with MM should be performed using latex-free products owing to the increased prevalence of latex sensitivity/allergy in these patients.

Another consideration in newborn males is circumcision. Because most children with MM eventually require intermittent catheterization, there may be an advantage of circumcision, facilitating access to the meatus. This procedure is helpful to the family initially and is particularly helpful to the boy as he assumes the responsibility for self-catheterization. Cultural preferences must always be considered. Many of the families of the authors' patients are Hispanic and generally prefer not to have circumcision performed in the newborn period.

From the outset, the goals of urologic management are (1) to minimize damage to the upper tracts and bladder from consequences of the neurologic deficit and (2) to minimize the social disabilities resulting from neurogenic bladder dysfunction. In early childhood, the greatest risk is from elevated intravesical pressure, which is directly measured urodynamically or indirectly suspected by the development of bladder trabeculation and upper tract changes on serial radiologic imaging. After baseline imaging studies are obtained and spontaneous bladder emptying is established, the next consideration is whether to perform urodynamic testing.

Urodynamic evaluation

Background and controversies

In 1981, McGuire et al [3] observed that upper tract changes occurred when intravesical pressure during filling or the time of leakage exceeded 40 cm H_2O. They further noted that the cause of elevated pressure was fixed outlet resistance from denervation of the external sphincter, resulting in bladder outlet obstruction (although the possibility that bladder denervation alone created hypertonicity was also considered). This mechanism explained the common observation on serial radiologic imaging that an initially smooth-walled bladder could become markedly trabeculated and assume a vertically oriented "Christmas tree" configuration as the bladder hypertrophied, lost compliance and capacity, and developed hyperreflexia from obstruction. As is true in other causes of outlet obstruction, these secondary changes potentially are reversible or even avoidable by performing therapy to lower intravesical pressure. Based on this observation, patients with MM can be classified into high- and low-risk groups based on their detrusor leak point pressure (DLPP).

Over the following decade, urodynamic testing became an integral part of the initial evaluation and subsequent management of newborns with MM in many tertiary centers. Patients with presumably high-risk parameters, including a DLPP greater than 40 cm H_2O or detrusor sphincter dyssynergia, typically are prescribed anticholinergic medications and begun on intermittent catheterization at diagnosis before secondary damage occurs. Advocates justify this approach to minimize the deleterious effects of high intravesical pressure, noting that, in more than 50% of patients who are observed with periodic radiologic imaging, febrile urinary tract infection (UTI), hydronephrosis, or reflux develops by 3 years of age [2]. Furthermore, the Boston group reported that newborn urodynamics were predictive of patient outcomes. Eighty percent of infants believed to be at high risk experienced upper tract changes when followed up expectantly [4].

Recent studies suggest that early intervention may protect not only the upper tracts but the bladder as well, diminishing the eventual need for augmentation. Kaefer et al [5] compared high-risk patients followed expectantly with a subsequent group undergoing early intervention and found

that the augmentation rate decreased from 41% to 17%. Wu et al [1] similarly noted fewer augmentations when children began therapy for high intravesical pressure during the first year of life. Proponents add the observation (generally by consensus) that because nearly all children with MM eventually require intermittent catheterization for continence, its early introduction increases patient and family understanding and acceptance.

The alternative to urodynamic-based management is serial radiologic imaging to detect secondary evidence of high bladder pressure. Proponents suggest that close monitoring with prompt intervention for signs of deterioration is effective in protecting the upper tracts. Although febrile UTI, hydronephrosis, or reflux may develop during observation, intervention when such problems occur has resulted in deterioration in only 1% to 5% of renal units [2,6]. These studies defined "renal deterioration" largely based on anatomic changes. To date, no one has reported the use of serial nuclear renography in urodynamic or radiologic-based management protocols.

Critics of newborn urodynamics note a lack of standards for the performance and interpretation of the test, which may lead to unnecessary interventions. McGuire et al [3] reported that reflux and hydronephrosis occurred almost exclusively in patients with a DLPP greater than 40 cm H_2O determined by "slow filling" cystometry. Joseph [7] subsequently emphasized the importance of the infusion rate in DLPP determination. He found that filling rates of 20% of estimated bladder capacity per minute were more often associated with a DLPP greater than 40 cm when compared with 2% infusion rates in the same patients. The lack of uniformity in the filling rates published in series of urodynamic evaluations in children is important. Before intervention for a presumably elevated DLPP is initiated, these technical factors should be considered. Decter and Harpster [8] found that the DLPP was also influenced by urethral catheter size and gravity drip versus infusion pump filling.

The difficulty in accurately determining the DLPP can be inferred from the observation that as many as 20% of presumably high-risk patients have remained stable without upper tract changes on observation [4]. Perhaps the true intravesical pressure was not as high as the pressure measured during testing, or the testing was done when the spinal cord function was still in flux. Even when the DLPP is accurately determined to be elevated, upper tract deterioration can develop despite intermittent catheterization and anticholinergic medication [1,9]. Detrusor compliance may be so poor that periodic catheterization does not keep pressures low, or persistently high storage pressures may occur at night when the bladder is not emptied. Prophylactic intermittent catheterization would treat some patients unnecessarily (ie, those with a falsely elevated DLPP) yet not prevent problems in others. Furthermore, as discussed later, the urodynamic pattern can change over time, with conversion of a low-risk DLPP to one greater than 40 cm H_2O, raising questions regarding the best timing for initial and follow-up studies if a urodynamic protocol is recommended.

To the authors' knowledge, no study has investigated patient and family acceptance of intermittent catheterization based on the age at which it is instituted. Certainly, the catheterization of infants increases demands on the family, and access to health care providers who can perform intermittent catheterization is less available in day-care facilities than in the public school system. Enthusiasm for the process also wanes if small volumes routinely are obtained, causing the parents to question its usefulness. In general, it is the authors' impression that parents accept catheterization when it is medically necessary, or when it is recommended as a step toward urinary continence, especially if they have been counseled previously that catheterization would be instituted around the usual time of toilet training.

Despite these controversies regarding urodynamic evaluations, many centers, including that of the authors, manage infants with newborn testing and preemptive intervention. Until controlled studies comparing management strategies are available, well-done urodynamic tests should help to identify most patients at risk, and preemptive therapy in these cases may prevent many adverse effects from the neurologic deficit. Anecdotally, as older patients have entered the authors' interdisciplinary program, reviews of previous films have occasionally documented upper tract changes with loss of renal function occurring despite periodic imaging. When looking longitudinally at interventions and responses, any program must acknowledge the additional concern that patients managed in a "watchful waiting" program inevitably can be lost to follow-up.

Newborn urodynamics

Initial urodynamic testing is performed soon after the spinal shock from back closure resolves,

usually around 6 weeks of age. At the authors' center, these studies are performed under physician supervision after a dedicated urodynamic nurse explains the details of the procedure to the family. A 5F urodynamic catheter is passed transurethrally, and a rectal balloon is placed for intra-abdominal pressure measurements. Contrast medium or saline is infused via a pump with a filling rate based on 10% of estimated bladder capacity (approximately 5 mL/min). Perineal patch electrodes are commonly used to provide an estimation of external sphincter activity. Although a more accurate determination may be obtained by placing a concentric needle directly into the sphincter muscle, the technical logistics and patient tolerance can be offsetting factors. For baseline studies, the authors use intermittent fluoroscopy to image the bladder outlet and determine the pressure at which reflux, if present, occurs. Despite the use of rectal balloons to subtract intra-abdominal pressure, tests performed in an agitated infant are difficult to interpret. Several fillings may be needed to verify the findings, and an attempt should be made to obtain at least one tracing with the infant calm.

Findings

Few studies have attempted to characterize urodynamic findings in newborns with MM, and differences in reporting make comparisons difficult (Table 1). Twelve percent [10] to 32% of patients [11,12] had normal studies. In the remaining patients, detrusor contractility was noted in 40% to 76%; the rest were areflexic with preserved or diminished compliance. The external sphincter had normal electromyographic (EMG) activity in approximately 40% of infants but otherwise showed evidence of partial or complete denervation.

When present, detrusor–sphincter activity was characterized as synergic in 16% to 30% of infants and dyssynergic in 10% to 54%. Two studies [12,13] were performed using larger catheters (7F) with faster infusion rates (10 to 30 mL/min) than currently recommended for infants. In a more recent report, Sillen et al [12] used 6F catheters and infusion rates of 1.6 to 8 mL/min. Spindel et al [13] and Sidi et al [11] determined external sphincter activity with concentric needle electrodes. Sillen et al [12] used patch electrodes, which, in their laboratory, gave such poor EMG readings that sphincter activity could not be accurately defined.

The finding that as many as one third of infants had normal urodynamics and many of the remainder had detrusor contractility and external sphincter activity is in contrast to reported evaluations in older children. In a follow-up study (mean, 7 years), McGuire et al [3] found that most of their older patients with MM had detrusor areflexia, decreased compliance, and fixed outlet resistance from sphincter denervation. These differing observations suggest that the neurourologic status of children with MM can change over time.

The changing urodynamic pattern in myelomeningocele

Spindel et al [13] first reported neurourologic changes in children detected by serial urodynamic testing, which occurred in 37% of patients during the first 3 years of life and usually within the first 12 months. Specifically, they evaluated external sphincter activity and found evidence of new or progressive denervation in half of the cases, whereas the other half showed improved innervation. They speculated that the improvement might have indicated recovery from spinal shock after back closure in some cases and reinnervation in others. The patients with deterioration had radiologic findings of a tethered cord. A subsequent study at this institution reported that neurosurgical intervention resulted in improvement or stabilization of urodynamic findings in 90% of children in whom it was performed [14]. Overall, the risk of deterioration leading to consideration for additional neurosurgery was 10% during the first year of life. Among the infants initially found to have normal external sphincter innervation, partial or complete denervation developed in 27%, whereas 46% of patients with detrusor–sphincter synergy at birth later had dyssynergy.

Other researchers have focused attention on detrusor responses without detailed EMG characterization of sphincter activity. Roach et al [15] found that 32% of infants with an initially low DLPP and normal upper tracts converted to a high DLPP within 6 months. Sillen et al [12], performing the urodynamic testing at ages 1, 4, and 10 months, found that 40% of patients experienced changes, typically with worsening compliance, which occurred most often between 1 and 4 months.

The risk of neurourologic deterioration is perhaps best exemplified by a study of 25 newborns with normal urodynamics [10]. Initial assessment was done at approximately 14 days of age, when neurologic examination suggested resolution of spinal shock from back closure. Follow-up urodynamic studies were performed

Table 1
Urodynamics in newborns with MM

Urodynamic techniques						Findings		
Study	Number of patients	Catheter (F)	Infusion rate	Fluoroscopy	External sphincter EMG	Bladder	External sphincter EMG	Detrusor–sphincter activity
Sidi et al [11] 1986	30	7	10–15mL/min (CO^2)	No	Needle	12, Reflexic	11, Normal	9, Synergy
						18, Acontractile 3 Normal compliance 15 Decreased compliance	15, LMN	3, DSD
Spindel et al [13] 1987	79	7	15–30mL/min	No	Needle		38, Normal 18, Partial LMN 23, Complete LMN	13, Synergy 43, DSD 23, No sphincter activity
Lais et al [14] 1993	148[a]	Not stated	10% EBV/min	No	Needle		60, Normal 35, Partial LMN 53, Complete LMN	28, Synergy 67, DSD 53, No sphincter activity
Sillen et al [12] 1996	34	6	1.6–8mL/min	No	Skin patch	11, Normal reflexic		
						15, Hyperreflexic	Poor quality	11, Outlet Obstruction
						8, Acontractile		

Abbreviations: EBV, estimated bladder volume; DSD, detrusor–sphincter dyssynergia; LMN, lower motor neuron.

[a] Includes 79 previously reported by Spindel et al [13].

annually. Deterioration occurred in 40% of patients, all within 6 years of age. In most cases, urodynamic studies detected these changes before radiologic or neurologic examinations. Subsequent spinal cord detethering restored normal function in 25%. The researchers emphasized that early diagnosis is required for detethering to reverse changes, presumably before irreversible ischemia of the cord occurs. The patients who remained stable during follow-up were ambulatory, voided spontaneously, and achieved satisfactory urinary and fecal continence.

Despite differences in the timing and methodology of these urodynamic studies, it is reasonable to conclude the neurourologic status changes in some patients, often within the first 12 months of life. Of greatest concern is the loss of external sphincter innervation, because this, in turn, may result in fixed elevated outlet resistance and subsequent bladder deterioration. The observation that neurosurgical intervention restores function in some cases potentially increases the responsibility of the urologist to detect changes in urodynamics, because these changes often precede other clinical signs of cord tethering. Nevertheless, performing the test too early after closure of the spinal cord lesion may confuse interpretation, because spinal shock may not have resolved. It also remains unclear when optimal follow-up testing should be performed, and the nature of the "window of opportunity" for detethering to restore changing detrusor–sphincter function remains undefined. Longitudinal, controlled, multisite studies are needed to define these parameters.

Treatment

High-risk infants, that is, those with a DLPP greater than 40 cm H_2O or detrusor–sphincter dyssenergia, are started on a regimen of 0.2 mg/kg/dose of oxybutynin twice daily and intermittent catheterization every 3 hours throughout the day. In many cases, catheterization at least once during the night (as the infant awakens for feedings) is also recommended. Urodynamic studies are repeated, usually without fluoroscopy, 6 weeks later to verify a sufficient anticholinergic response and to compare routine volumes obtained during catheterization at home with safe storage volumes determined by testing. It has then been the authors' practice to monitor these children with renal sonography every 6 months and VCUG annually for the next several years. Urodynamic studies are repeated if new hydronephrosis, reflux, or unexplained febrile UTIs develop.

Vesicostomy, done more often in the past, is another option for early management of high intravesical pressure. It has become apparent that families usually can safely manage infants with intermittent catheterization. Indications for vesicostomy include intolerance to anticholinergic medication or the failure of pharmacotherapy to improve detrusor compliance sufficiently and maintain low storage pressure despite every 2- to 3-hour catheterization. Rarely, surgery is performed because the parents are unable to perform catheterization owing to their work schedules or other social considerations.

Infants with a low DLPP on initial urodynamic studies most often are left on diaper drainage without intermittent catheterization. These patients also are followed up with renal sonography and VCUG at age 6 months. Renal and bladder sonograms are obtained annually. Urodynamic studies are not repeated on a scheduled basis but are reserved for infants in whom upper tract deterioration or febrile UTIs develop. Nevertheless, some infants with low-risk findings convert to a high DLPP. If close frequent clinical monitoring by an interdisciplinary team is not available, another option would be to repeat urodynamic testing, perhaps at 6 or 12 months of age, because radiologic changes lag behind urodynamic findings.

Reflux in patients with MM often indicates high intravesical pressure, and therapy to lower pressure may resolve it. Antibiotic prophylaxis is used in children who have upper tract changes of reflux or hydronephrosis. Bacteriuria occurs in 60% to 80% of children with MM and neurogenic bladders and typically does not require intervention. Recurring febrile UTI has been estimated to occur in approximately 20% of patients. With recent US Food and Drug Administration approval of dextranomer/hyaluronic acid, endoscopic injection is another option for management if reflux persists despite lowering intravesical pressure, or if UTI occurs despite trials on prophylactic antibiotics.

Bacteriuria is found in 60% to 80% of children with MM, especially in those undergoing intermittent catheterization. Typically, these patients are asymptomatic, and those with low bladder pressure and routine emptying regimens are not likely to have febrile infection. Asymptomatic bacilluria usually does not require antibiotic therapy, and children who are prescribed frequent courses of antibiotics are at increased risk for acquiring

resistant organisms that are more difficult to eradicate if symptoms develop.

Latex precautions

Latex allergic reactions in patients with myelomeningocele were first reported in the 1980s. Depending on the medical center, latex education programs, and hospital policies for providing a latex-free environment, the prevalence of children with MM and latex allergies ranges from 35% to 75%. All children with MM should be considered at risk for the development of latex allergies, and avoidance of exposures to latex should be a high priority for families and health care professionals. The Spina Bifida Association of America provides regularly updated lists of common objects (in the community and medical/dental settings) that contain latex and alternative products that can be readily substituted. Updated versions for offices, hospitals, and parent education can be obtained at www.sbaa.org.

Summary

Few children with MM are born with and maintain normal bladder and sphincter function. Most urodynamic evaluations in the first months of life indicate abnormal innervation of these structures. Deterioration with the development of fixed external sphincter resistance, loss of detrusor compliance, and decreased capacity occurs in some patients within months to a few years of age. The DLPP helps distinguish patients at greater risk for subsequent upper tract damage from elevated intravesical pressure, despite the inherent imprecision of the tests. Nevertheless, some infants with low-risk assessments show upper tract deterioration over time. The optimal timing of initial and follow-up urodynamic studies remains controversial. Radiologic surveillance is considered by some an adequate alternative to early urodynamic studies, based on the observation that hydronephrosis and reflux detected by imaging most often resolve with medical management.

The Boston group has focused attention on function of the external sphincter and the potential for denervation to occur over time, placing the bladder and upper tracts at increased risk. Their experience suggests that needle electrodes, rather than patches, should be used for EMG during urodynamic studies to best evaluate sphincter innervation. It remains unproved whether the early detection of external sphincter denervation with subsequent spinal cord detethering will improve long-term outcomes over the current management philosophy in other centers, which emphasizes control of elevated bladder pressure.

Despite advances in the urologic care of children with MM, many basic questions regarding optimal evaluation and management remain unanswered. Regardless of whether management is primarily based on urodynamics (with preemptive intervention), radiologic imaging (with intervention for development of adverse changes), or a combination of the two, all children with MM require close surveillance for urologic problems, especially during the first few years of life. Goals to protect the bladder and upper tracts and eventually to attain continence, ideally by school age, are discussed with the family from the outset and reinforced during periodic follow-up visits.

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A practical approach to intersex in the newborn period

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The evaluation and management of a newborn with ambiguous genitalia must be undertaken immediately and with great sensitivity. The pediatric urologist, in conjunction with an endocrinologist, geneticist, and child psychiatrist, should work closely with the family in pursuing a dual goal: (1) to establish the correct diagnosis of the intersex abnormality and (2) with input from the parents, to assign a gender based on the diagnosis and the child's anatomy. This article outlines a practical approach to the neonate born with intersex.

Diagnosis

An individual's chromosomal sex is established at fertilization whereupon the undifferentiated gonads develop into either testes or ovaries. A patient's phenotypic sex results from the differentiation of internal ducts and external genitalia under the influence of hormones and transcription factors. Any discordance among these processes results in ambiguous genitalia or intersexuality. Currently, there are four main categories of intersex: female pseudohermaphroditism; gonadal dysgenesis, either pure or mixed; true hermaphroditism; and male pseudohermaphroditism [1–3].

Female pseudohermaphroditism

Patients affected with female pseudohermaphroditism, the most common intersex disorder, are 46,XX with normal ovaries and müllerian derivatives. The sexual ambiguity is limited to virilization of the external genitalia that occurs as a result of exposure to androgens in utero. Congenital adrenal hyperplasia (CAH), which accounts for most patients with female pseudohermaphroditism, describes a group of autosomal recessive disorders that arises from a deficiency in one of five genes required for the synthesis of cortisol (Fig. 1). These five genes and the enzymes they encode are as follows: *CYP21*, 21-hydroxylase; *CYP11*, 11β-hydroxylase, 18-hydroxylase, and 18-oxidase; *CYP 17*, 17α-hydroxylase and 17,20-lyase; *3β2HSD*, 3β-hydroxysteroid dehydrogenase; and *StAR*, side chain cleavage enzyme. Although these biochemical defects are characterized by impaired cortisol secretion, only deficiencies in *CYP21* and *CYP11* are predominantly virilizing disorders, with *3β2HSD* deficiency to a lesser extent. Although the female fetus is masculinized owing to overproduction of adrenal androgens and precursors, affected males have no genital abnormalities. In contrast, *3β2HSD*, *CYP17*, and *StAR* deficiencies block cortisol synthesis and gonadal steroid production; therefore, affected males have varying degrees of male pseudohermaphroditism, whereas females generally have normal external genitalia [4–6]. CAH resulting in male pseudohermaphroditism is discussed in detail later in this article.

The most common cause of CAH is inactivation of *CYP21*, which catalyzes the conversion of 17-OH progesterone to 11-deoxycortisol, a precursor of cortisol, and the conversion of progesterone to deoxycorticosterone (DOC), a precursor of aldosterone. A spectrum of phenotypes ranging from mild to severe clitoromegaly is possible. Classic

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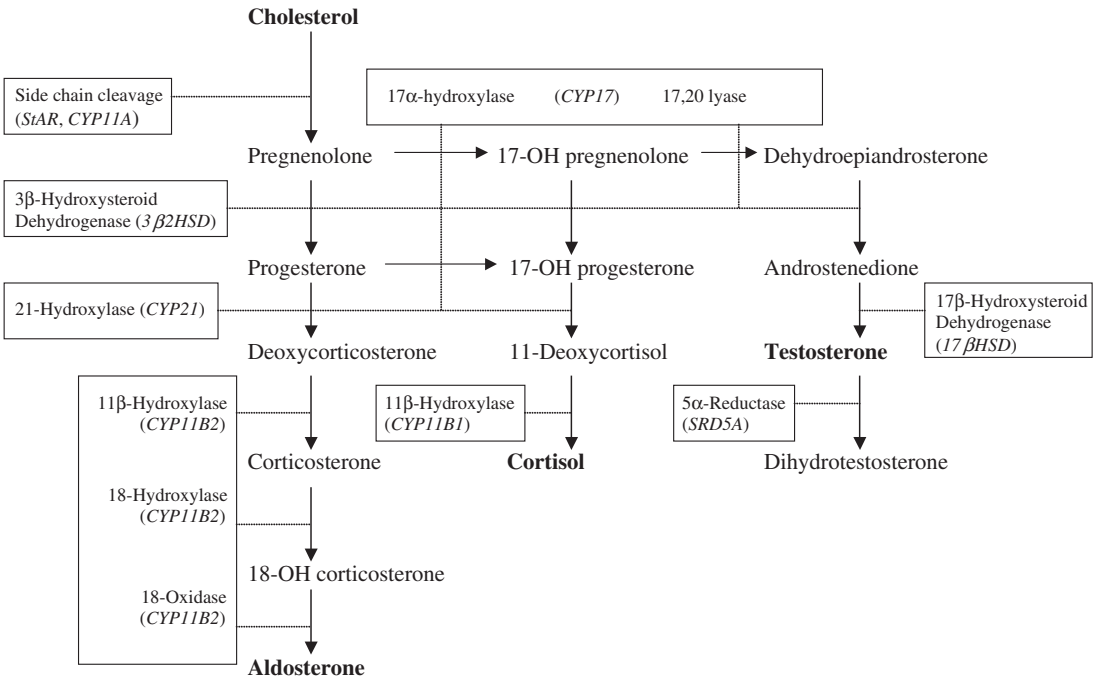


Fig. 1. Cholesterol–steroid biosynthesis pathway. Enzymes are listed in boxes and genes in parentheses.

21-hydroxylase deficiency comprises two forms of CAH: a severe salt-wasting type with a defect in aldosterone biosynthesis and a simple virilizing type with normal aldosterone synthesis. A mild nonclassic form also exists that can be asymptomatic or associated with signs of postnatal androgen excess [7]. There are two *CYP11* genes, *CYP11B1* and *CYP11B2*. *CYP11B1* converts 11-deoxycortisol to cortisol [8,9]. Alternatively, *CYP11B2* converts DOC to corticosterone, corticosterone to 18-hydroxycorticosterone, and 18-hydroxycorticosterone to aldosterone. Hypertension, which occurs in about two thirds of patients, is presumptively a consequence of excess DOC, with resultant salt and water retention. Excess androgen secretion in utero masculinizes the external genitalia of the female fetus. After birth, untreated males and females progressively virilize and experience rapid somatic growth and skeletal maturation.

3β2HSD catalyzes three reactions: pregnenolone to progesterone, 17-OH pregnenolone to 17-OH progesterone, and dehydroepiandrosterone (DHEA) into androstenedione [6]. Complete deficiency of *3β2HSD* impairs synthesis of adrenal aldosterone and cortisol and gonadal testosterone and estradiol. These newborns have severe CAH and exhibit signs of mineralocorticoid and glucocorticoid deficiency in the first week of life. Virilization occurs because of DHEA conversion to testosterone in fetal placenta and peripheral tissues, manifesting as mild-to-moderate clitoromegaly.

CYP17 also catalyzes three reactions: pregnenolone to 17-OH pregnenolone, 17-OH pregnenolone to DHEA, and progesterone to 17-OH progesterone [6]. Phenotypically, affected females have normal internal and external genitalia but demonstrate sexual infantilism owing to an inability of the ovaries to secrete estrogens at puberty. In mild defects, aldosterone secretion may be normal and hypertension absent [10].

Also called lipoid adrenal hyperplasia, *StAR* deficiency is a rare form of CAH and is the most severe genetic defect in steroidogenesis. It is associated with severe glucocorticoid and mineralocorticoid deficiencies owing to the failure to transport cholesterol from the outer to the inner mitochondrial membrane, which blocks conversion of cholesterol to pregnenolone [11]. Affected females demonstrate normal internal and external genitalia. Many patients die in infancy; approximately 33% survive with replacement therapy.

Gonadal dysgenesis

Mixed gonadal dysgenesis is the next most common intersex disorder. In general, gonadal

dysgenesis disorders comprise a spectrum of anomalies ranging from complete absence of gonadal development to delayed gonadal failure owing to abnormalities of sex or autosomal chromosomes. The lack of proper development into a testis or an ovary leads to a dysgenetic testis or streak gonad.

Pure gonadal dysgenesis describes a 46,XX child with streak gonads or, more commonly, a child with Turner syndrome (45,XX or 45,XX/46,XX). 45,XX/46,XX mosaicism may be seen in up to 75% of patients with Turner syndrome [12]. An uncommon form of pure gonadal dysgenesis is called Swyer syndrome. This child looks female externally and has a uterus and fallopian tubes; however, the karyotype is 46,XY with a Y chromosome that usually does not work and two dysgenetic gonads in the abdomen [13].

Partial gonadal dysgenesis refers to disorders with partial testicular development, including mixed gonadal dysgenesis, dysgenetic male pseudohermaphroditism, and some forms of testicular or ovarian regression. Mixed or partial gonadal dysgenesis (45,XX/46,XY or 46,XY) involves a streak gonad on one side and a testis, often dysgenetic, on the other side. A patient with a Y chromosome in the karyotype is at a higher risk than the general population to develop a tumor in the streak or dysgenetic gonad. Gonadoblastoma, a benign growth, is the most common tumor [14]. Because of the 20% to 25% age-related risk of malignant transformation into a dysgerminoma [15], surgical removal of the gonad is recommended. The patient with a 45,XX/46,XY karyotype and normal testis biopsy could retain the testis if it is descended or can be placed in the scrotum. This child would then need to perform close follow-up of the testis by monthly self-examinations to detect tumor formation.

True hermaphroditism

True hermaphroditism requires expression of ovarian and testicular tissue, resulting from sex chromosome mosaicism, chimerism, or a Y-chromosome translocation. The most common karyotype in the United States is 46,XX, although 46,XY or mosaicism or chimerism (46,XX/46,XY) can occur. Mosaicism may occur from chromosomal nondisjunction, whereas chimerism may result from a double fertilization (an X and a Y sperm) or from fusion of two fertilized eggs. Some patients with 46,XX true hermaphroditism have the *SRY* gene translocated from the Y to the X chromosome; however, for most patients, the genes responsible are not yet identified [16,17]. This uncommon condition can be classified further into three groups. Individuals with lateral true hermaphroditism have a testis on one side and an ovary on the contralateral (usually left) side. Individuals with bilateral true hermaphroditism have an ovotestis on each side. Individuals with unilateral true hermaphroditism, the most common subgroup, have an ovotestis on one side and either a testis or an ovary on the contralateral side. Furthermore, the external genitalia are ambiguous, with hypospadias, cryptorchidism, and incomplete fusion of the labioscrotal folds. The genital duct differentiation in these patients generally follows that of the ipsilateral gonad on that side, such as a fallopian tube with an ovary and a vas deferens with a testis [18].

Male pseudohermaphroditism

Male pseudohermaphroditism is a heterogeneous disorder in which the testes are present, but the internal ducts system or the external genitalia are incompletely masculinized. The phenotype is variable and ranges from completely female external genitalia to the mild male phenotype of isolated hypospadias or cryptorchidism. Male pseudohermaphroditism can be classified into eight basic etiologic categories: (1) Leydig cell failure, (2) testosterone biosynthesis defects, (3) androgen insensitivity syndrome, (4) 5*a*-reductase deficiency, (5) persistent müllerian duct syndrome (PMDS), (6) testicular dysgenesis, (7) primary testicular failure or vanishing testes syndrome, and (8) exogenous insults.

Leydig cell failure

The presence of testosterone, produced by testicular Leydig cells, induces male differentiation of the wolffian ducts and external genitalia. Male pseudohermaphroditism can result from Leydig cell unresponsiveness to human chorionic gonadotropin hormone (hCG) and luteinizing hormone (LH). The phenotypes of these patients range from normal female to hypoplastic external male genitalia.

Testosterone biosynthesis enzyme defects

Described earlier in this article in the section on female pseudohermaphroditism, defects in four of the steps of the steroid biosynthetic pathway from cholesterol to testosterone may also produce genital ambiguity in the male [5,6]. These defects include the less common forms of CAH: *3β2HSD* deficiency, *CYP17* deficiency, *StAR* protein deficiency, and *17βHSD* deficiency. Although DHEA

conversion into testosterone results in virilization in females, this same process insufficiently masculinizes affected males. Male infants exhibit ambiguous genitalia with variable degrees of hypospadias, cryptorchidism, penoscrotal transposition, and a blind vaginal pouch. Males with *CYP17* deficiency display a developmental spectrum ranging from the normal female phenotype to the ambiguous hypospadiac male [10,19]. The magnitude of the decreased masculinization in the male infant correlates with the severity of the block in 17α-hydroxylation. Affected males with *StAR* deficiency have severe testosterone deficiencies and exhibit female external genitalia with a blind vaginal pouch [20,21]. No surviving 46,XY patient has demonstrated testis function at puberty. The affected 46,XY males with *17βHSD* deficiency have external female genitalia, inguinal testes, internal male ducts, and a blind vaginal pouch. At puberty, these patients demonstrate an increase in their levels of gonadotropins, androstenedione, estrone, and testosterone. Delayed virilization may ensue if some testosterone levels approach the normal range [22,23].

Androgen insensitivity syndrome

The broad spectrum of androgen insensitivity syndrome ranges from 46,XY patients with complete androgen insensitivity syndrome, or testicular feminization, to partial androgen insensitivity syndrome. This syndrome is the result of mutations of the steroid-binding domain of the androgen receptor, resulting in receptors unable to bind androgens or receptors that bind androgens but exhibit qualitative abnormalities and do not function properly. This disorder affects 1 in 20,000 live male births with a maternal inheritance pattern, because the androgen receptor gene is located on the long arm of the X chromosome [24].

The external genitalia of a child with complete androgen insensitivity resemble that of a normal female, although the karyotype is XY, and testes are located internally. Historically, these children have been raised as girls. Most children are not diagnosed until puberty during an evaluation for primary amenorrhea. Occasionally, it is discovered at the time of inguinal hernia repair or, more recently, when the prenatal karyotype does not match the external phenotype of the newborn child.

5α-Reductase deficiency

5α-Reductase deficiency was first described as pseudovaginal perineal scrotal hypospadias [25]. In this autosomal recessive condition, patients have a defect in the conversion of testosterone to dihydrotestosterone (DHT). These patients have a 46,XY karyotype and ambiguous external genitalia but normally differentiated testes with male internal ducts. At puberty, significant virilization occurs as testosterone levels increase into the adult male range while DHT levels remain disproportionately low. Three genetic isolates of this disorder have been described in the Dominican Republic, the New Guinea Samba Tribe, and Turkey. Many of these patients undergo a change of their gender identity from female to male after puberty [26,27]. Virilization can be secondary to slightly increased plasma DHT levels and the chronic effect of adult testosterone levels on the androgen receptor.

Persistent müllerian duct syndrome

Antimüllerian hormone, or müllerian inhibitory substance, is secreted by the Sertoli cells from the time of fetal seminiferous tubule differentiation until puberty. Müllerian inhibitory substance binds to a receptor in the mesenchyme surrounding the müllerian ducts before 8 weeks' gestation, causing apoptosis and regression of the müllerian duct [28]. Because the diagnosis of PMDS is often made at the time of inguinal hernia repair or orchiopexy, this syndrome is commonly referred to as hernia uteri inguinali. PMDS can occur from a failure of the testes to synthesize or secrete müllerian inhibitory substance owing to an *AMH* gene mutation, or from a defect in the response of the duct to müllerian inhibitory substance owing to an *AMH2* receptor gene mutation. PMDS is inherited in a sex-linked autosomal recessive manner. *AMH* mutations are most common in Mediterranean or Arab countries with high rates of consanguinity [29]. Most of these familial mutations are homozygous, and the patients have low or undetectable levels of serum müllerian inhibitory substance. In contrast, *AMH2* receptor mutations are often heterozygous and are more common in France and Northern Europe. These patients usually have high-normal or elevated müllerian inhibitory substance concentrations [12].

Testicular dysgenesis

Individuals with dysgenetic male pseudohermaphroditism exhibit ambiguous development of the internal genital ducts, the urogenital sinus, and the external genitalia. Dysgenetic testes can result from mutations or deletions of any of the genes involved in the testis determination cascade, namely

SRY, DAX, WT1, and *SOX9*. The *SRY* gene is a single exon gene located on the short arm of the Y chromosome [30]. *SRY* gene mutations usually result in complete gonadal dysgenesis and XY sex reversal or Swyer syndrome. The DSS locus (dosage sensitive sex reversal) has been mapped to the Xp21 region that contains the *DAX1* gene. Duplication of the DSS locus has been associated with dysgenetic male pseudohermaphroditism and other anomalies. The DSS locus has been theorized to contain a wolffian inhibitory factor that acts as an inhibitory gene of the testis determination pathway [31]. Swain et al [32] have shown that *DAX1* antagonizes *SRY* action in mammalian sex determination. Male patients with Denys-Drash syndrome have ambiguous genitalia with streak or dysgenetic gonads, progressive nephropathy, and Wilms' tumor. Analysis of these patients has revealed heterozygous mutations of the Wilms' tumor suppressor gene (*WT1*) at 11p13 [33]. The WAGR syndrome (Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation) is also associated with *WT1* alterations [34]. The genitourinary anomalies seen in the WAGR syndrome are usually less severe than in Denys-Drash syndrome. The *SOX9* gene has been associated with campomelic dysplasia, an often lethal skeletal malformation with dysgenetic male pseudohermaphroditism [35]. Affected 46,XY males have phenotypic variability ranging from normal males to normal females depending on the function of the gonads.

Congenital anorchia

Congenital anorchia or vanishing testes syndrome encompasses a spectrum of anomalies resulting from cessation of testicular function [36]. A loss of the testes before 8 weeks' gestation results in 46,XY patients with female external and internal genitalia and either no gonads or streak gonads. A loss of the testes at 8 to 10 weeks in development leads to ambiguous genitalia and variable ductal development. A loss of testis function after the critical male differentiation period at 12 to 14 weeks' gestation results in a normal male phenotype externally along with anorchia internally. Sporadic and familial forms of anorchia exist. The familial cases, including some reports of monozygotic twins, support the presence of an as yet unidentified mutant gene in some patients with the syndrome.

Exogenous source

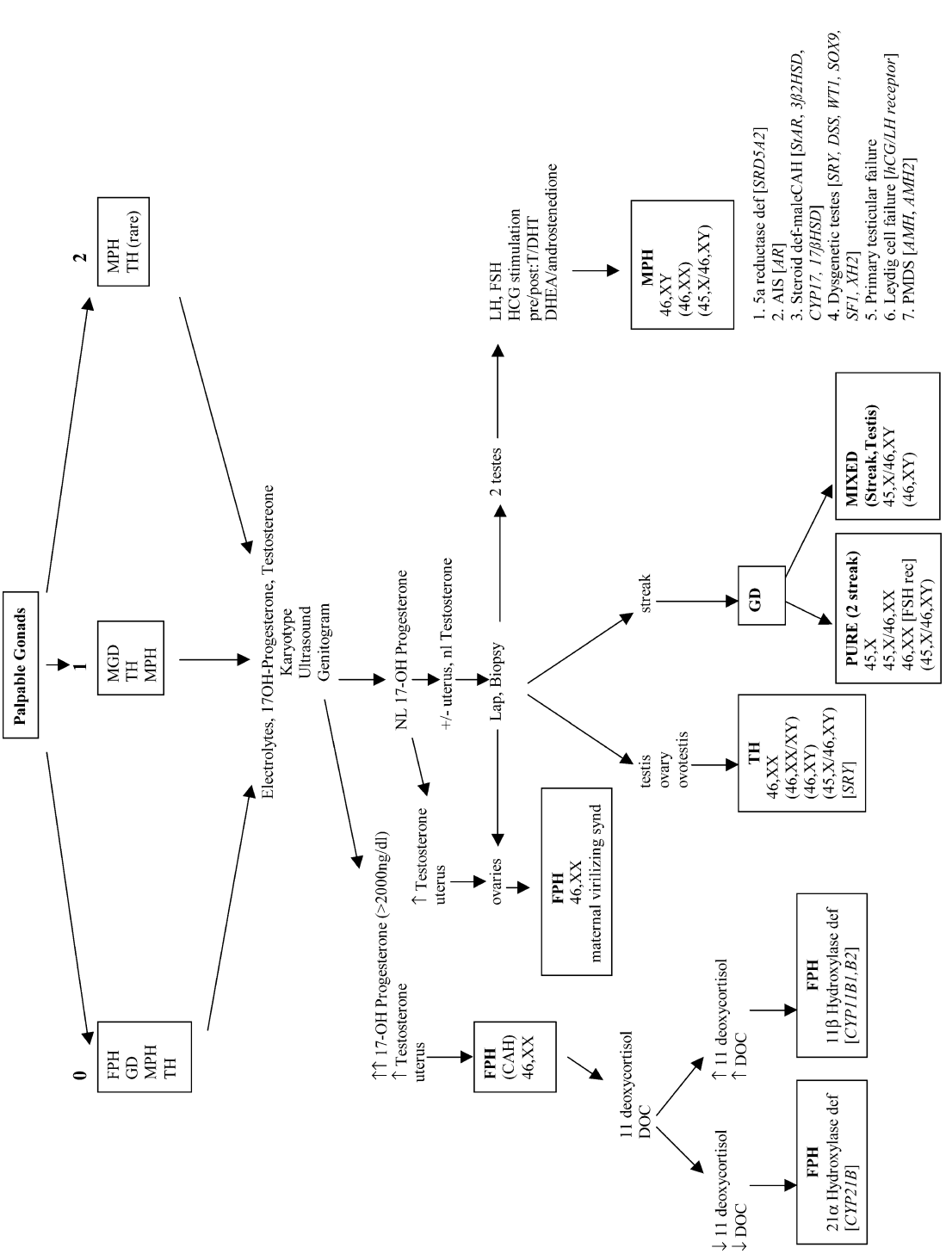
Exogenous insults to normal male development include the maternal ingestion of progesterone or estrogen or various environmental hazards. As early as 1942, Courrier and Jost [37] demonstrated an antiandrogen effect on the male fetus induced by a synthetic progestagen. More recently, Silver et al [38] showed an increased incidence of hypospadias in male offspring conceived by in vitro fertilization. They hypothesized that the increased risk may be secondary to maternal progesterone ingestion. Sharpe and Skakkebaek [39] have further postulated that the increase in reproductive abnormalities in men is related to an increase in the in utero exposure to environmental estrogens.

Sex chromosome anomalies

Sex chromosome anomalies comprise another category of patients with intersexuality. Klinefelter's syndrome (47,XXY) usually becomes evident during adolescence as the patient presents with gynecomastia, variable androgen deficiency, and small atrophic testes with hyalinization of the seminiferous tubules. These patients demonstrate azoospermia and increasing gonadotropin levels. 47,XXY males may develop through nondisjunction of the sex chromosomes during the first or second meiotic division in either parent or, less commonly, through mitotic nondisjunction in the zygote at or after fertilization. These abnormalities almost always occur in parents with normal sex chromosomes. 46,XY/47,XXY mosaicism is the most common form of the Klinefelter variants. Patients with the mosaic forms, in general, manifest a much milder phenotype than do classic Klinefelter patients. Testes differentiation and a lack of ovarian development in these patients indicate that a single Y chromosome with *SRY* expression is enough for testis organogenesis and male sex differentiation in the presence of as many as four X chromosomes in some Klinefelter patients. These testes are not truly normal, because they are usually small and azoospermic. Although there are sporadic reports of paternity, most fertile Klinefelter individuals have sex chromosome mosaicism [40–42].

Sex reversal

Categories of 46,XX sex reversal include classic XX male individuals with apparently normal phenotypes, nonclassic XX males with some degree of sexual ambiguity, and XX true hermaphrodites [43]. Eighty percent to 90% of 46,XX males result from an anomalous Y to X translocation involving the *SRY* gene during meiosis. In general, the


Palpable Gonads
0
FPH
GD
MPH
TH
1
MGD
TH
MPH
2
MPH
TH (rare)
Electrolytes, 17OH-Progesterone, Testostereone
Karyotype
Ultrasound
Genitogram
↑↑ 17-OH Progesterone (>2000ng/dl)
↑ Testosterone
uterus
FPH
(CAH)
46,XX
↑ Testosterone
uterus
ovaries
NL 17-OH Progesterone
+/- uterus, nl Testosterone
Lap, Biopsy
2 testes
LH, FSH
HCG stimulation
pre/post:T/DHT
DHEA/androstenedione
MPH
46,XY
(46,XX)
(45,X/46,XY)
FPH
46,XX
maternal virilizing synd
11 deoxycortisol
DOC
testis
ovary
ovotestis
streak
TH
46,XX
(46,XX/XY)
(46,XY)
(45,X/46,XY)
[SRY]
GD
PURE (2 streak)
45,X
45,X/46,XX
46,XX [FSH rec]
(45,X/46,XY)
MIXED
(Streak,Testis)
45,X/46,XY
(46,XY)
↓ 11 deoxycortisol
↓ DOC
FPH
21α Hydroxylase def
[CYP21B]
↑ 11 deoxycortisol
↑ DOC
FPH
11β Hydroxylase def
[CYP11B1,B2]
1. 5a reductase def [SRD5A2]
2. AIS [AR]
3. Steroid def-maleCAH [StAR, 3β2HSD, CYP17, 17βHSD]
4. Dysgenetic testes [SRY, DSS, WT1, SOX9, SF1, XH2]
5. Primary testicular failure
6. Leydig cell failure [hCG/LH receptor]
7. PMDS [AMH, AMH2]

greater the amount of Y-chromosome DNA present, the more virilized is the phenotype. Although 8% to 20% of XX males have no detectable Y sequences, including *SRY*, about 1 in 20,000 phenotypic males have a 46,XX karyotype. Most of these patients have ambiguous genitalia, but reports of classic XX males without the *SRY* gene exist [31,43,44]. This phenomenon again raises the possibility of mutation of a downstream wolffian inhibitory factor when cases of normal virilization are seen without the presence of the *SRY* gene.

History and physical examination

The patient with bilaterally impalpable testes or a unilaterally impalpable testis and hypospadias should be regarded as having an intersex disorder until proven otherwise, regardless of whether the genitalia appear ambiguous. Patient history should include the level, if any, of prematurity, the ingestion of exogenous maternal hormones, such as those used in assisted reproductive techniques, and the maternal use of oral contraceptives during pregnancy. A family history is also useful to screen for any urologic abnormalities, neonatal deaths, precocious puberty, amenorrhea, infertility, or consanguinity. Any abnormal virilization or cushingoid appearance of the child's mother should be noted. Abnormalities seen on prenatal maternal ultrasound are also helpful, such as discordance of the fetal karyotype with the genitalia by sonogram.

For differential diagnosis and treatment purposes, the most important physical finding is the presence of one or two gonads. If no gonads are palpable, all four categories are possible (female pseudohermaphroditism, male pseudohermaphroditism, gonadal dysgenesis, or true hermaphroditism). Of these entities, female pseudohermaphroditism is most commonly seen, followed by mixed gonadal dysgenesis. A palpable gonad is highly suggestive of a testis or, rarely, an ovotestis, because ovaries and streak gonads do not descend. If one gonad is palpable, female pseudohermaphroditism and pure gonadal dysgenesis are ruled out, whereas mixed gonadal dysgenesis, true hermaphroditism, and male pseudohermaphroditism remain possibilities. If two gonads are palpable, male pseudohermaphroditism and, rarely, true hermaphroditism are the most likely diagnoses (Fig. 2).

The patient should be examined in a warm room and placed supine in the frog leg position with both legs free. It is important to check the size, location, and texture of both gonads, if palpable. The undescended testis may be found in the inguinal canal, the superficial inguinal pouch, at the upper scrotum, or, rarely, in the femoral, perineal, or contralateral scrotal regions. One should also note the development and pigmentation of the labioscrotal folds along with any other congenital anomalies of other body systems. An abnormal phallic size should be documented by width and stretched length measurements. One should describe the position of the urethral meatus and the amount of chordee and note the number of orifices.

Another critical finding on physical examination is the presence of a uterus, which is palpable by digital rectal examination as an anterior midline cordlike structure. A thorough general physical examination should not be overlooked. Dysmorphic features indicating syndromic manifestations, such as a short broad neck, widely spaced nipples, or aniridia, should also be noted.

Patient evaluation

In the immediate newborn period, all patients require a karyotype and laboratory evaluation, including assays for serum electrolytes, 17-OH progesterone, testosterone, LH, and follicle-stimulating hormone (FSH). Once the karyotype is determined, serum analysis will assist in narrowing the differential diagnosis. If the 17-OH progesterone level is elevated, a diagnosis of CAH can be made. Determining the levels of 11-deoxycortisol and deoxycorticosterone will help differentiate between 21-hydroxylase and 11β-hydroxylase deficiencies. If the levels are elevated, a diagnosis of 11β-hydroxylase deficiency can be made, whereas low levels confirm 21-hydroxylase deficiency. If the 17-OH progesterone level is normal, determination of a testosterone to DHT ratio along with androgen precursors before and after hCG stimulation will help elucidate the cause of male pseudohermaphroditism. A failure to respond to hCG in combination with elevated LH and FSH levels is consistent with anorchia. The examiner should remember that, for the first 60 to 90 days of life, a normal gonadotropic surge

Fig. 2. Intersex flowchart. Genes are listed in italics and uncommon karyotypes in parentheses. AIS, androgen insensitivity syndrome; FPH, female pseudohermaphroditism; GD, gonadal dysgenesis; MGD, mixed gonadal dysgenesis; MPH, male pseudohermaphroditism; T/DHT, testosterone/dihydrotestosterone; TH, true hermaphroditism.

occurs with a resultant increase in the testosterone level and its precursors. During this specific period, hCG stimulation for androgen evaluation can be postponed.

Radiographic tests

Noninvasive, quick, and inexpensive, an ultrasound should be the first radiologic examination performed. Although it is only 50% accurate in detecting intra-abdominal testes [45], ultrasound can detect gonads in the inguinal region and can assess müllerian anatomy. Although they are more expensive, a CT scan and MR imaging scan can further delineate the anatomy. A genitogram should be performed to evaluate a urogenital sinus, including the entry of the urethra in the vagina and the presence of a cervical impression [45]. Infants with intra-abdominal or nonpalpable testes in whom true hermaphroditism, mixed gonadal dysgenesis, or male pseudohermaphroditism is considered will require an open or laparoscopic exploration with bilateral deep longitudinal gonadal biopsies for histologic evaluation, which will determine the presence of ovotestes, streak gonads, or dysgenetic testes, thereby confirming the diagnosis. This procedure is a diagnostic maneuver. Removal of gonads or reproductive organs should be deferred until the final pathology report is available, a diagnosis is achieved, a discussion has occurred between the family and all consultants, and a gender decision is reached [46].

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Hypospadias

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Hypospadias results from abnormal development of the penis that leaves the urethral meatus proximal to its normal glanular position anywhere along the penile shaft, scrotum, or perineum. A spectrum of abnormalities, including ventral curvature of the penis (chordee), flattening of the glans penis, "hooded" incomplete prepuce, and an abortive corpora spongiosum, is associated commonly with hypospadias.

John W. Duckett, Jr, the former chief of the Division of Urology at the Children's Hospital of Philadelphia (CHOP), coined the term *hypospadiology* and distinguished himself as a pioneer in the field. Pediatric urologists worldwide recognize hypospadiology as an evolving and expanding discipline that remains at the forefront of pediatric surgical innovation. Although modern experiments have begun to yield a deeper understanding of the genetic, hormonal, and environmental basis of hypospadias, the quest for a surgical procedure that consistently results in a straight penis with a normally placed glanular meatus has challenged surgeons for over two centuries. Advances in the understanding of the etiology of hypospadias and the current approaches to the correction of hypospadias to provide a cosmetically and functionally satisfactory repair are the focus of this article.

Etiology

Understanding of the embryologic development of the penis confirms that hypospadias results from partial or complete failure of urethral folds to form throughout their normal length. Hypospadias also may result if urethral folds that have formed fail to close distally; the extent of the closure determines the position of the urethral orifice.

A unifying etiology for hypospadias remains elusive and is likely multifactorial. Current reports expand on the early observations by Devine and Horton [1] that hypospadias results from incomplete embryologic development as a result of: (1) abnormal androgen production by the fetal testis, (2) limited androgen sensitivity in target tissues of the developing genitalia, or (3) premature cessation of androgenic stimulation caused by early atrophy of the Leydig cells of the testes.

Endocrine factors

Hypospadias is believed to be a mild form of intersexuality; hypospadias could represent one end of a spectrum, the other of which is a completely feminized male [2,3]. Hypospadias may result from an endocrinopathy in which there is a disruption in the synthetic biopathway of androgens. More than just a focal malformation, hypospadias may be a local manifestation of a systemic endocrinopathy. A qualitative androgen-receptor abnormality or defects at a postreceptor level may explain the defect in some boys with hypospadias.

For example, the blunted response to human chorionic gondadotropin (hCG) injections seen in many boys with hypospadias may suggest a mutation in the luteinizing-hormone receptor in the testis or an increase in receptor numbers as

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a consequence of the previous stimulation [3]. In a study by Allen and Griffin [3] of 15 boys (less than 4 years of age) with severe hypospadias, six distinct endocrine-related abnormalities were diagnosed among 11 boys. The most consistent finding was a subnormal testosterone response to hCG stimulation in seven boys. The authors postulated that their findings may represent a delay in the maturation of the hypothalamic-pituitary-testicular axis.

Genetic factors

Hypospadias is believed to have a complex genetic background, with altered gene expression resulting from an interaction of transcriptional mutations acting in concert with environmental factors. The familial rate of hypospadias is approximately 7%, reflecting a nonfamilial, sporadic finding in most cases. Recent studies have suggested a role for Mullerian-inhibiting substance (MIS) in the etiology of hypospadias. There is an inverse relationship between MIS and testosterone, and this may be related to the MIS inhibition of cytochrome P450c17 (*CYP17*), the enzyme that catalyzes the committed step in testosterone synthesis [4]. MIS may inhibit directly testosterone production by suppressing the *CYP17* gene [5]. Abnormalities of other genes, such as fibroblast growth factor-10, also result in hypospadias [6].

Normal sexual differentiation depends on testosterone and its metabolites as well as functional androgen receptors. There is a correlation of certain clear defects in the androgen metabolism pathway with hypospadias, as in the 5α-reductase defect (mutation in *SRD5A2* gene on chromosome 2) [7]. The limited associations that have been described, however, underline the importance of seeking other genetic explanations for this congenital defect [7].

Environmental factors

The rise in the incidence of hypospadias has heightened concern that globally ubiquitous environmental contaminants may be contributing factors. Insecticides, pharmaceuticals, and plant estrogens contain estrogenic ingredients, and metal cans used in the canned-food industry are coated internally with plastics containing estrogenic substances [6]. These substances have become ubiquitous in the environment and are present in fresh and sea water in trace amounts. Predators at the top of the food chain, such as large fish, birds, sea mammals, and humans, subsequently bioaccumulate and concentrate these estrogenic environmental contaminants. Thus, humans and wild animals are exposed constantly to estrogenic compounds know to disrupt reproduction—the so-called "endocrine disrupters" [6].

Maternal factors

In 1967 Goldman and Bongiovanni [8] suggested a role for maternal progestin exposure in the development of hypospadias. These researchers produced hypospadias in male rats by experimentally inducing congenital adrenal hyperplasia. A disturbance in the maternal-fetal hormonal milieu as a causative factor in humans was substantiated when male offspring conceived by in vitro fertilization requiring progestin therapy had a markedly increased incidence of hypospadias [9,10]. Fredell and colleagues [11] associated low birth weight with hypospadias in discordant monozygotic twins.

Future areas of research

Studies that elucidate the role of cellular signals other than testosterone and dihydrotestosterone in normal phallic development and hypospadias, endocrine disrupters, and mesenchymal-epithelial interaction, may hold the key to explaining the etiology of hypospadias [6]. Research in the areas of homeobox gene also may open new avenues toward increased understanding of the cause of hypospadias.

Epidemiology

The incidence of hypospadias is rising and varies geographically. Prevalence ranges from 0.26 per 1000 births (male and female births) in Mexico to 2.11 in Hungary and 2.6 per 1000 live births in Scandinavia [12]. The rate of hypospadias in a recent 2-year prospective study was 38 per 10,000 live births in the Netherlands, six times higher than previously recorded [13]. In 1974 Sweet and colleagues [14] reported a much lower incidence in Sweden of 1 in 1250 live male births.

In 1997, two independent surveillance systems in the United States, the nationwide Birth Defects Monitoring Program (BDMP) and the Metropolitan Atlanta Congenital Defects Program (MACDP), reported a nearly doubling rate of hypospadias when compared with immediately preceding decades [15]. The incidence of all types of hypospadias increased from 20.2 to 39.7 per 10,000 live male births from 1970 to 1993 (ie, 1 in

every 250 live male births was a boy with hypospadias [measured by BDMP]). MACDP reported a rise in the severe hypospadias rate of between threefold and fivefold. These trends, however, simply may reflect earlier diagnosis or an increase in reporting to registries of congenital defects. The increased reporting of more proximal than distal hypospadias cases, however, refutes the argument that these findings represent more frequent reporting of minor cases [16].

Recent studies have linked the rising rate of hypospadias to boys born prematurely and small for gestational age, boys with low birth weight, and boys born to mothers over 35 years of age [17–19]. Roberts and Lloyd noted an 8.5-fold increase in hypospadias in one of monozygotic male twins, compared with singleton live male births [20]. This may suggest a discrepancy in the supply of hCG to the fetus where a single placenta is unable to meet the requirements of two developing male fetuses.

Chordee

Chordee is the ventral penile curvature that accompanies hypospadias in some cases. It is seen more commonly in severe cases of hypospadias, but also can occur independent of hypospadias. Study of penile development through examination of fetal specimens has led to the understanding that chordee is a normal stage in penile development, and that significant variation in the severity of chordee was noted at all stages of embryogenesis.

If chordee is an arrest of normal embryologic development analogous to failure of descent of the testicle, it is no surprise that fibrosis is conspicuously absent in some clinical cases of chordee [21,22]. Snodgrass and colleagues [23] recently supported this finding further, demonstrating that all subepithelial biopsies of urethral plate examined under a microscope showed well-vascularized connective tissue comprised of smooth muscle and collagen without evidence of fibrous bands or dysplastic tissue. Baskin and colleagues [24] found well-vascularized connective tissue under the epithelial surface of the urethral plate in a 33-week fetus with distal hypospadias.

In some patients, chordee is present without hypospadias. Devine and colleagues [25] described three types of chordee without hypospadias. In class I, the most severe defect, the corpus spongiosum is deficient from the site at which the chordee begins, up to the glans, whereas the urethra has a thin tube of mucous membrane. In class II, the urethra has a normal corpus spongiosum with abnormal Buck's fascia and dartos fascia layers. In class III, only the dartos fascia layer is abnormal.

Associated findings

Cryptorchidism and inguinal hernia

Between 8% to 10% of boys with hypospadias have a cryptorchid testicle and 9% to 15% have an associated inguinal hernia [26,14,27]. In boys with more proximal hypospadias, cryptorchidism may occur as frequently as 32% [28]. This strong association between proximal hypospadias and undescended testis further suggests that this clinical entity may represent one end of a spectrum of endocrinopathy. The incidence of chromosomal anomaly in these groups of patients is much higher (22%) than hypospadias (5%–7%) or cryptorchidism (3%–6%) occurring alone [29,30].

Intersexuality

Hypospadias and intersexuality also are believed to represent two ends of a spectrum [2]. The more severe the hypospadias, the more likely an intersex state exists [31]. Rajfer and Walsh [32] reported intersexuality in 27.3% of boys with a normal-sized phallus, cryptorchidism, and hypospadias. Presence of severe hypospadias and nonpalpable testes with otherwise normal-looking phallus requires that the urologist test for the presence of an intersex state [31].

Partial androgen insensitivity, chromosomal abnormalities, Smith-Lemli-Opitz syndrome, 5α-reductase deficiency, Drash syndrome, and other conditions also can occur in association with hypospadias.

Prostatic utricle

The prostatic utricle is an elementary structure developing from Mullerian ducts cranially and from the Wollfian ducts and the urogenital sinus caudally [33]. Boys with hypospadias often have enlargement of prostatic utricle with resultant urinary tract infections, stone formation, pseudo-incontinence and, often, difficult catheterization [34–36]). Devine and colleagues [37] reported that 57% of the patients with perineal hypospadias and 10% with penoscrotal hypospadias had prostatic utricle enlargement demonstrated on urethroscopy. The overall incidence of utricle enlargement in patients with hypospadias was 14% in this series of 44 patients. Utricular

enlargement does not itself indicate an intersex state, but is seen with increased frequency in patients with male pseudohermaphroditism.

Presentation

The abnormal prepuce and ventral glans tilt of the newborn penis usually signifies the presence of hypospadias. Further examination of the penis typically reveals the proximally displaced urethral orifice that is often stenotic in appearance, but rarely obstructive. An exception is the megameatus variant of hypospadias. In this unusual case (6% of all distal hypospadias presentations), an intact prepuce is present. The diagnosis usually is not made until after a routine neonatal circumcision is completed [38].

The anatomic location of the meatus and extent of ventral curvature, or chordee, should be determined. In some instances, multiple pinpoint dimples may be present on the surface of the urethral plate in addition to the hypospadiac urethral meatus. The meatus is always the most proximal of these defects and can be confirmed by physical examination or with passage of a probe. Meatal position may be classified as *anterior* (distal), *middle*, and *posterior* (proximal), with more anatomically specific subgroups being applied further (Fig. 1). The meatus is located on the glans or distal shaft of the penis in approximately 70% to 80% of boys with hypospadias. The meatus is located in the middle of the shaft of the penis in 20% to 30% of boys with hypospadias. The remainder of boys with hypospadias has more severe defects, with the urethral meatus located in the scrotum, or even more proximally on the perineum [39].

Increased understanding of the endocrinologic origins of hypospadias has corroborated the clinical association of hypospadias with intersex states [32,40]. As such, boys with severe proximal hypospadias and those with hypospadias and cryptorchidism should undergo karyotype analysis and an intersex evaluation as indicated. The unilaterality or bilaterality of cryptorchidism concomitant with hypospadias does not predict the diagnosis of an intersex state.

A complete penile examination requires independent evaluation of penile length even as the diagnosis of hypospadias is confirmed. If the stretched penile length is significantly below the third percentile for age, or if a clinical decision were made that inadequate phallic size would preclude adequate surgical repair of hypospadias, then androgen stimulation as pretreatment should be considered. Koff and Jayanthi [41] showed that androgenic pretreatment with hCG may increase penile length and move the meatus to a relatively more distal position as the shaft elongates in response to the hCG.

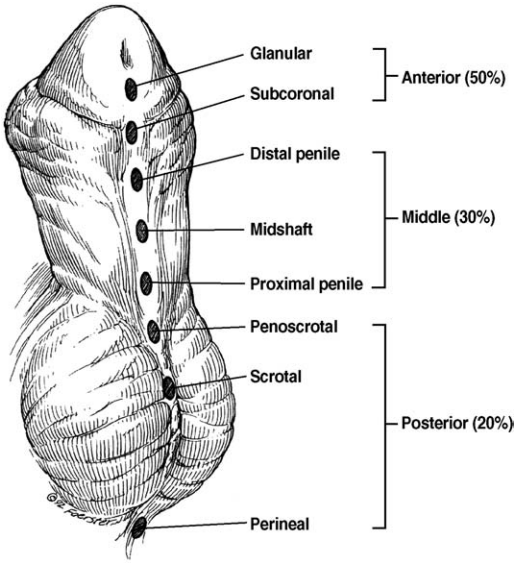

Fig. 1. Classification of hypospadias based on anatomic location of the urethral meatus. Anterior, or distal, hypospadias is the most commonly encountered variant. (*From* Duckett JW. Successful hypospadias repair. Contemp Urol 1992;4:42–55; with permission.)

Surgical repair

The goal of hypospadias surgery is a functional sexual organ that is free of curvature. Equally important is a glanular urethral meatus that allows a boy to void with a laminar flow while standing. A cosmetically sound penis requires a cone-shaped glans and supple penile shaft skin.

Timing of surgery

Experience over the past decade confirmed the American Academy of Pediatrics' review that the ideal age for genital surgery is between 6 to 12 months of age [42]. This age range seems to insulate most children from the psychologic, physiologic, and anesthetic trauma associated with hypospadias surgery. The authors prefer to operate on boys with proximal hypospadias and an adequately sized phallus even earlier, at 4 months of age, if there are no associated medical problems. Healing seems to occur more quickly

and with fewer scars, and young infants overcome the stress of surgery more easily.

Instruments

Increasing experience has demonstrated the applicability of the principles of plastic surgery to hypospadiology. Instruments such as fine scissors, 0.5-mm tooth forceps, and Castroviejo needle holders are used commonly with fine 6-0 or 7-0 absorbable sutures to handle tissue delicately and place sutures with precision. Surgeons vary in their choice of suture material. The authors prefer polygycolic suture material for construction of the neourethra and for buried sutures, and use a glanular stay suture to minimize tissue handling during repair. Polydiaxanone suture is not recommended for urethral repair because of its extended absorption time interval and increased urethral stricture rate [43].

Hemostasis

Adequate hemostasis may be achieved by various techniques in hypospadias surgery. Some surgeons place at the base of the penis a tourniquet that is removed every 45 minutes alone or combined with needlepoint spot and bipolar electrocoagulation to control blood loss that may obscure the surgical field. The authors minimize the use of electrocautery to reduce the potential for tissue damage from cautery dispersal and instead inject 1:100000 epinephrine in 1% lidocaine along the proposed incision line. In the authors' experience, the epinephrine provides adequate local hemostasis and the injection separates the skin and dartos that facilitates the initial dissection.

Dressing and urinary diversion

The ideal posthypospadias repair dressing provides adequate, pliable compression and is removed easily. Surgeons use numerous variations of dressing, and some use no dressing [44,45]. The authors prefer the "sandwich" dressing preferred by Duckett that compresses the penis against the lower abdominal wall by placing a Telfa pad and a folded gauze sponge on top of the penis followed by a bio-occlusive dressing (Tegaderm, 3M, St. Paul, Minnesota).

Urinary diversion often is preferred following proximal and midshaft hypospadias repairs, but its utility in distal repairs is based on surgeon preference rather than proven benefit. A multicenter experience reported by Hakim and colleagues [46] revealed similar results for distal repairs with or without postoperative urethral diversion. The authors place a 6-F hydrophilic Kendall catheter through the neourethra, with the tip just inside the bladder neck and sutured to the glans with a prolene suture anchored to the inner aspect of the meatus to avoid scarring of the glans. Because the rate of urinary infection is no different between an open and closed system as long as the drainage is ensured, the authors allow the open end of the Kendall tube to drain passively into the outer of two diapers [47].

Types of hypospadias repairs

A plethora of surgical options, from novel approaches to modifications of known procedures, have been described for various presentations of hypospadias. The surgical technique that is most appropriate for a given case is predicated heavily on anatomic factors, previous surgical descriptions, and a surgeon's personal experience.

Historically, surgeons have described hypospadias repairs as primary closures, metal-based flaps, dorsally based flaps, and free grafts. Conceptual advances, such as incision of the urethral plate with primary closure, have affected profoundly the current approach to hypospadias repair. The authors would like to share the techniques for hypospadias repair implemented at their institution over the past 30 years, with an understanding that these descriptions are templates. These procedures form a foundation that are modified, amplified, and reinvented to repair each boy's unique anatomy—the basis of evolution in hypospadiology.

Distal hypospadias

Meatal advancement, glanuloplasty

Meatal advancement, glanuloplasty (MAGPI) offers reliable cosmesis and long-term success when applied to glanular and selected coronal meatus repairs. Presence of urethral mobility and a rounded glans, along with the absence of significant chordee, should be established to ensure an ideal outcome and avoid meatal regression. Urethral mobility can be assessed adequately by distal traction on the meatus with fine forceps.

The MAGPI begins with a circumferential incision 6 to 8 mm proximal to the corona of the glans and proximal to the meatus (Fig. 2). Penile-shaft skin is dissected in a "drop-back" fashion with extreme care exercised ventrally over

the corpus spongiosum to avoid urethral injury. Residual chordee or penile torsion may be corrected at this point. A longitudinal incision from the dorsal distal edge of meatus is carried to the distal glans groove as it transects the transverse bridge of tissue that is often present (see Fig. 2B). The incised tissue edges are approximated in a Heineke-Mikulicz fashion with 7-0 absorbable sutures to advance effectively the meatus distally (see Fig. 2C). The medial edge of the ventral meatus is then pulled distally and the exposed glans edges are trimmed and anastamosed to leave the glans with a cosmetically sound, rounded appearance (Fig. 3). The dorsal hood foreskin is

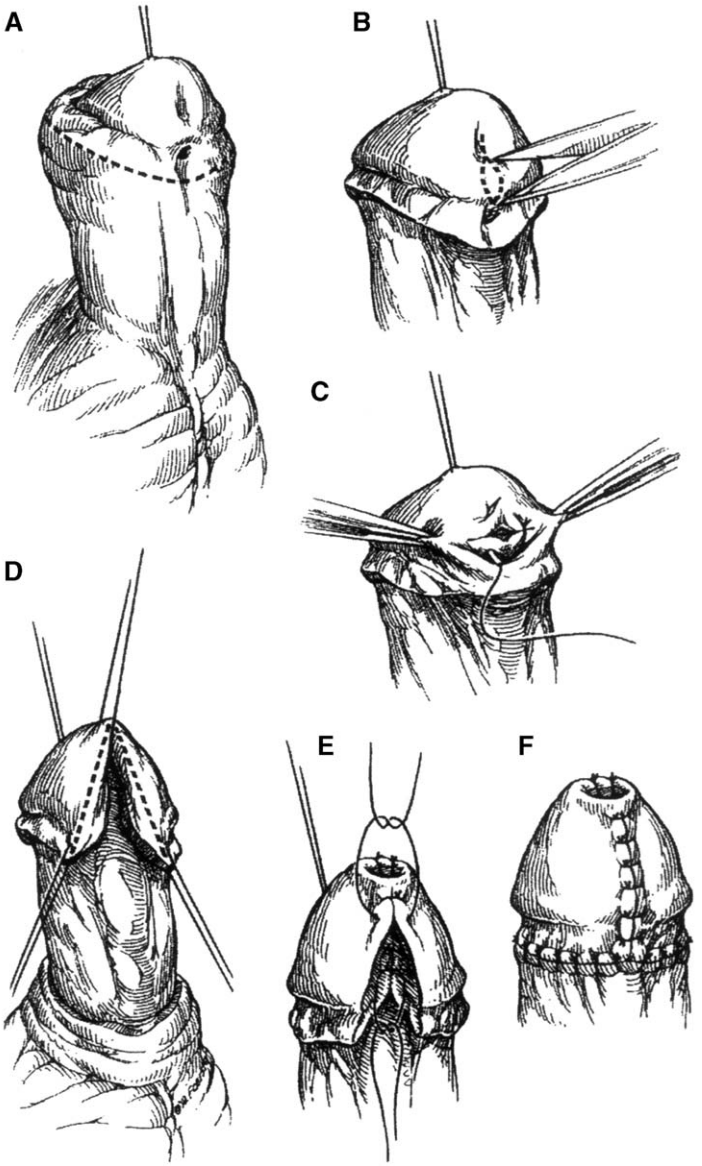

Fig. 2. Meatoplasty and glanuloplasty repair. (*A*) Circumferential incision 5 cm below the corona. (*B*) Transverse bridge of tissue distal to the meatus is incised sharply. (*C*) A Heinike-Mikulicz closure opens and advances the meatus. (*D*) Ventral meatal edge is pulled distally and the exposed glans edges are trimmed and approximated. (*E*) Glansplasty is performed with subepithelial sutures to leave a rounded, conical glans. (*F*) Dorsal skin is transferred ventrally, excess skin is excised and no catheter is left in place. (*From* Duckett JW. Successful hypospadias repair. Contemp Urol 1992;4:42–55; with permission.)

trimmed in the midline as Byar's flaps allow adequate ventral skin transfer, and skin is approximated to the glans with absorbable, subcuticular suture to complete the repair (Fig. 4).

Tubularized, incised plate urethroplasty

Recognizing that surgical repair of a hypospadias based on a flat urethral plate resulted in a horizontal, recessed meatus (in contrast to the cosmetically superior results when repairing a deeply grooved plate) Rich and colleagues [50] proposed the "hinging of the urethral plate" by incising it distally. Snodgrass [51] extended this concept by incising the plate deeply through the entire urethral plate to the corporal bodies, followed by a Thiersch-Duplay tubularization. A multicenter experience supported the concept and was followed by the application of tubularized, incised plate urethroplasty (TIP) to proximal hypospadias repairs [52,53].

A circumscribing skin incision is carried ventrally to 1 to 2 mm proximal to the urethral meatus and followed by skin drop-back to the penoscrotal junction (see Fig. 3A). Penile curvature is resolved and corrected by dorsal midline plication, if necessary. Two parallel longitudinal incisions in the glans allow lateral mobilization of the glans wings as care is taken not to undermine the vascularity of the urethral plate (see Fig. 3B).

The critical step in this repair involves a midline relaxing incision from within the meatus to the end of the urethral plate (see Fig. 3C). The incidence of meatal stenosis is reduced by limiting the incision to the actual plate and not incising the rim of the glans at the distal margin of the plate [54]. A 6-F stent is passed into the bladder and a two-layer, running subepithelial closure tubularizes the plate and creates a neourethra (see Fig. 3D). Subepithelial 6-0 polyglactin sutures approximate the glans wings beginning at the corona to complete a glansplasty (see Fig. 3F). The inherent disadvantage of superimposed suture lines with this closure may be countered by developing a dartos pedicle from dorsal shaft skin that is buttonholed and transposed to the ventrum (see Fig. 3E).

More proximal hypospadias cases are approached for a TIP repair by first incising the

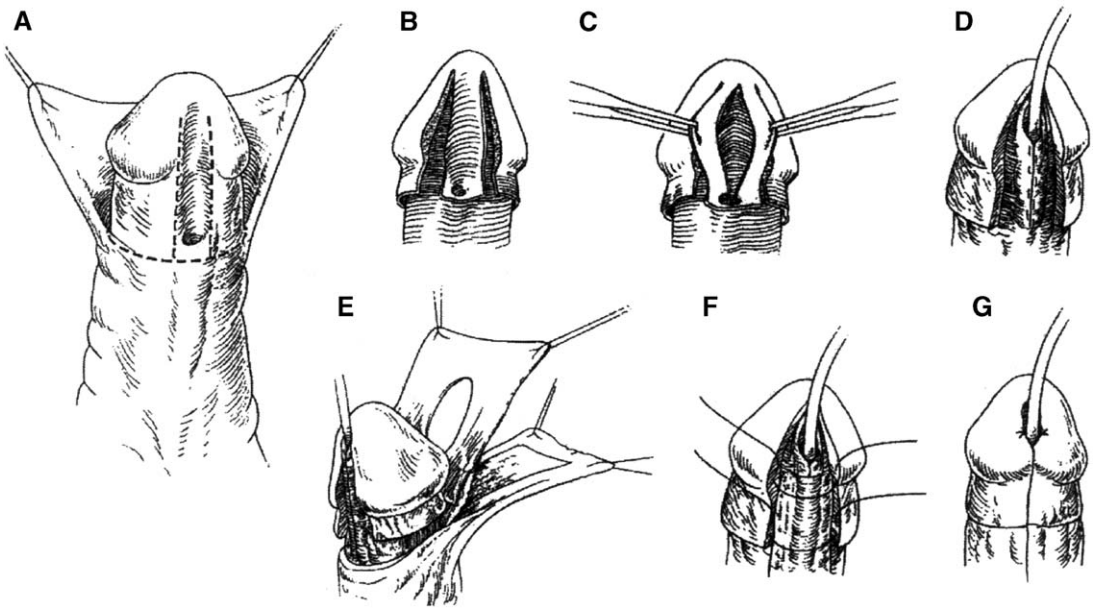

Fig. 3. Tubularized incised plate urethroplasty (TIP). (*A*) Circumscribing incision along dashed lines to deglove penis. (*B*) Glans wings mobilized laterally off the corpora cavernosa and separated from the urethral plate. (*C*) Longitudinal incision in the midline of the urethral plate. The incision widens the urethral plate. (*D*) Tubularization of urethral plate with a two-layer subepithelial approximation. (*E*) Dartos pedicle flap dissected off of the inner preputial skin and transposed ventrally to provide an additional cover over the suture line. (*F*) Glans wings are approximated in the midline with subepithelial sutures. (*G*) Meatus sewn to glans at two positions and urethral stent secured in place. (*From* Snodgrass WT, Nguyen MT. Current technique of tubularized incised plate hypospadias repair. Urology 2002;60:157; with permission.)

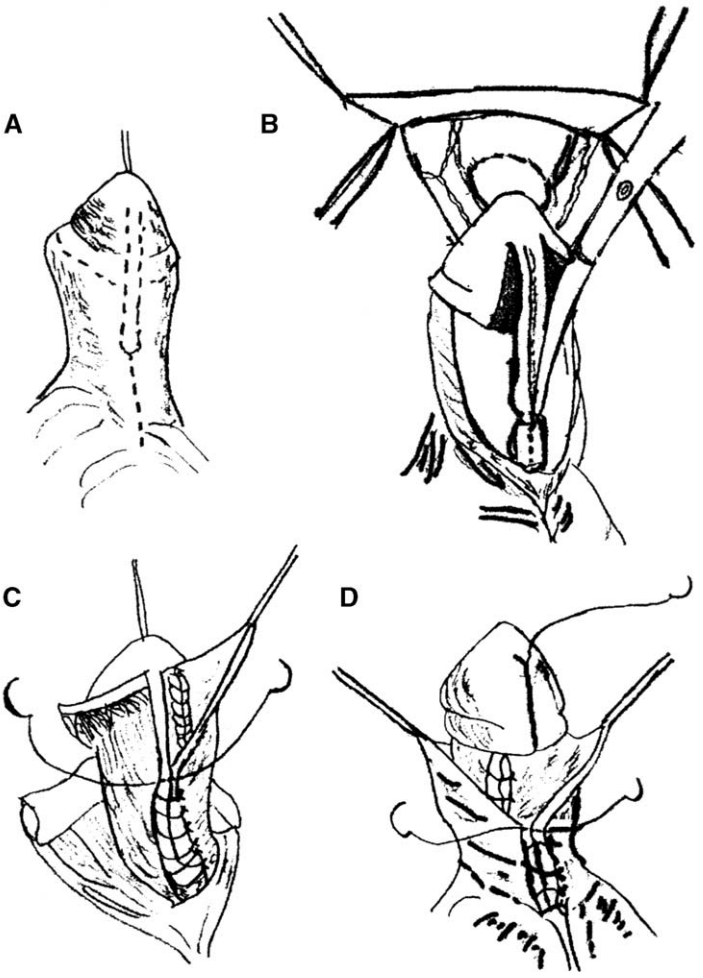

Fig. 4. Onlay island flap. (*A*) Dashed lines indicate initial circumcising incision carried along to the ventrum and anteriorly to provide a subcoronal collar (Firlit flap). The midline incision is carried to the penoscrotal junction to facilitate adequate inspection of spongiosal tissue. (*B*) Penis is degloved and the native urethral meatus is incised back to normal spongiosal tissue. Thin, gossamer-like dysplastic urethral tissue is incised until normal, well-vascularized tissue is seen. Stay sutures separate the inner and outer faces of the preputial flap and the onlay flap is mobilized with mesentery intact. A buttonhole in the mesentery allows ventral transposition without increasing torque on the penis. (*C*) The edges of the flap are sutured with subepithelial interrupted sutures. Proximal tailoring of the flap minimizes the risk for diverticulum formation. (*D*) Byars flaps cover the skin deficient ventrum with subcuticular sutures.

proximal plate and leaving the distal plate intact. If the urethral plate increases in width, as expected, then incising the distal plate continues the repair.

Middle and proximal hypospadias or distal hypospadias with chordee

Island onlay hypospadias repair

Van Hook first introduced the concept of a preputial flap based on a vascular pedicle to repair proximal hypospadias in 1896 [55]. Asopa and colleagues [56] developed the effective use of inner preputial skin for a substitution urethroplasty and Duckett [57] furthered this technique by describing a transverse preputial island flap (TPIF) repair in 1980. The island onlay flap evolved from the TPIF as experience demonstrated that repair of the chordee with hypospadias can be accomplished by dissection of the subcutaneous tissue and dorsal midline plication, and that division of the urethral plate is required in only

10% of cases [49]. The concept that spongiosum consists of vascularized tissue and smooth muscle bundles that may be used in a hypospadias repair evolved over the 1980s after histologic examination [23,48]. The onlay island flap is used for more than 90% of the authors' patients with subcoronal hypospadias.

The circumferential incision begins dorsally 6 to 8 mm proximal to the corona and is carried ventrally just proximal to the meatus (see Fig. 4A). The incision is then carried further proximally to split ventral shaft skin in the midline to the penoscrotal junction (see Fig. 4B). Parallel incisions 5 mm wide or narrower are then made along the urethral plate distally to the glans tip where the flat ventral surface of the glans begins to curve around the meatal groove. The skin and dartos fascia are dissected laterally as residual chordee is released. Dissection of the skin should preserve the intrinsic vascularity dermis to ensure its viability as a flap. If dissection of the penile ventrum reveals laterally displaced and thinned spongiosal tissue overlying the urethral tissue, which is common, the authors incise the urethra through the nearly transparent spongiosum proximally to what appears to be normal tissue. The urethral plate need not be more than 2 mm wide before the onlay transfer and is tailored narrower or wider depending on the glans configuration and size and depth of glans groove.

The island onlay flap is outlined on the inner preputial skin surface with interrupted 5-0 polypropylene sutures that also are used as stay sutures (see Fig. 4B). The sutures are grasped so that the fold of tissue between the inner and outer prepuce is accentuated. An 8- to 10-mm segment of this epithelium is divided sharply with the initial incision just beneath the skin at the junction between the inner and outer preputial faces of foreskin. The combined width of the preserved plate and the flap should be about 10 mm and no wider at the anastomosis between the neo and native urethra than at the urethral meatus.

The freeing of the vascular pedicle begins at the midshaft where it is separated most easily from the blood supply to the dorsal penile shaft skin. This approach to the harvest of the flap easily identifies the proper plane and ensures preservation of blood supply to the flap. In the authors' experience, the ventral midline incision of the penile-shaft skin completed during the initial circumcising skin incision releases the base of the dorsal vascular pedicle and allows the penile shaft skin to flatten. This provides better separation of the vascular pedicle from the dorsal preputial foreskin and penile-shaft skin.

After harvest, the island flap is rotated ventrally, or more commonly, transferred by creating a window in the vascular mesentery through which the glans is passed, and then trimmed to appropriate size (see Fig. 4C). The authors find that too wide a neourethra may lead to kinking or diverticulum formation. If the proximal end of the island flap is left the same width as the distal end, a diverticulum will form at the neo to native urethral anastomosis. The flap should be narrowed aggressively at the proximal end where the native urethra is spatulated to prevent a diverticulum. It also should be made no larger than the intended urethral caliber; 8 F for most 6-month-old boys. Using a flap that is oversized intentionally to allow for "shrinkage" is wrong. A well-vascularized flap does not narrow with time.

The appropriately designed flap is then sutured into place using lubricated, interrupted, 7-0 polyglactic sutures at the proximal meatus and then in an interrupted subepithelial fashion along the lateral edges of the plate (see Fig. 4C). The authors no longer close the flap over a feeding tube, instead preferring to place the tube at the conclusion of the construction of the neourethra. The 8-F feeding tube then serves as a spacer to ensure an adequately sized glansplasty. The glansplasty is completed by medial rotation of mobilized glans wings with 6-0 Maxon sutures placed parallel to the cut edge of the glans wing beginning at the urethral meatus (see Fig. 4D). A 6-F Kendall urethral stent is placed and the dorsal preputial skin is split in the midline and rotated ventrally to afford adequate circumferential skin coverage.

Transverse island tube repair

The transverse island tube repair remains the authors' preferred technique for boys with proximal hypospadias. This procedure incorporates inner preputial skin, as in the onlay technique, to be rolled completely into a neourethra without use of the urethral plate as a vascularized template. A "bulky" glansplasty, penile torque, and an "oval" rather than "slit-like" urethral meatus results in some cases, which the authors believe may have hampered popular use of the island tube in favor of a staged repair. Incorporating excessive preputial skin into a neourethra also has raised concern for forming a urethral diverticulum and turbulent flow. The authors have excellent long-term results with flap urethroplasties and chose to

address these concerns by modifying the original procedure rather than abandoning it in favor of a two-stage repair using transferred dorsal skin or a graft. The authors recently have described their modifications to this classic procedure that they believe address these cosmetic and functional problems [58], and describe them here.

A glans-holding suture is placed. A circumcising incision is outlined with a marker and extended on the midline to the penoscrotal junction. To ensure hemostasis, a solution in a ratio of 1:100000 epinephrine and 1% lidocaine is infiltrated along the marked line. The skin incision is then made and the penis is degloved superficial to Buck's fascia, beginning the dissection ventrally and extending from the urethral meatus to the penoscrotal junction and then dorsally to the penopubic junction. The urethra is opened proximally to healthy vascularized spongiosum as in the onlay repair. An artificial erection is performed, and the urethral plate is transected at the corona and dissected off of the corporal tissue if the penile curvature is persistent. The glans is incised deeply in the midline and excess epithelium is trimmed. Another artificial erection delineates the extent of residual penile curvature and a Heineke-Mikulicz incision made vertically and closed horizontally straightens the penis, if necessary, using 6-0 polydioxanone suture.

A segment of inner preputial tissue is harvested dorsally as described for the island onlay. The mesentery of the flap is buttonholed and then transposed ventrally. Rather than rolling the tissue into a tube at this point, as previously described, the authors first anchor one margin of the flap to the urethra proximally (Fig. 5). This maneuver allows the flap to be tailored optimally by stretching the skin to the opposite, anchored edge of the flap (see Fig. 5D). The tube can be fashioned to align properly the anastamosis to the native urethra and to construct a tube of ideal caliber. A second interrupted subcuticular suture line then rolls the tube effectively into the glans (see Fig. 5E).

A glansplasty is completed with 6-0 Maxon sutures placed parallel to the cut edge of the glans as a horizontal mattress to cover the distal edge of the tube. A 6-F urethral stent is placed and dorsal preputial skin is fashioned to provide adequate skin coverage as in all hypospadias repairs.

Two-stage repair

Anecdotal and reported experience has suggested that the two-stage technique may offer fewer overall complications and better cosmetic results than the single-stage repair for select cases [59,60]. In the authors' experience, however, there is a similar fistula rate following the second stage of a two-stage repair to that following a one-stage island onlay or tube repair, and the authors believe that with proper technique, equal or better results follow a single-stage urethroplasty. Nevertheless, the authors occasionally encounter challenging cases where severe chordee and a proximal meatus limit the applicability of a one-stage tube repair. In a few cases, injury to the vascular pedicle of the onlay or tube during harvest requires that the repair be staged.

A two-stage repair often involves a scrotoplasty with an aggressive attempt to relieve penile curvature, including transection and proximal removal of the plate. Either a dermal graft or tunica vaginalis may be interpositioned, although rarely in the authors' experience, to bridge any defect in the ventral tunica albuginea surface. Preputial skin at the dorsum is then split to rotate the resultant flaps ventrally. Alternatively, an island flap of skin can be harvested as described above and rotated into the ventrum of the penile shaft to reconstruct a "neourethral plate." These flaps are allowed to settle into place and represent the future urethral plate.

The second stage is planned after an interval of 6 to 12 months. At that time, parallel vertical incisions 12 to 15 mm apart are mapped distally, beginning at the meatus and including the glans. Glans wings are mobilized and the glans may be incised in the midline as with the TIP repair. Incisions are completed and a neourethra then is tubularized to complete the repair using a standard Thiersch-Duplay technique. The authors aggressively cover the repair with dartos tissue or, in some cases, with processus vaginalis flaps taken adjacent to the spermatic cord on one side or the other. In some cases, placement of the suture line into the scrotum facilitates healing. The penis is then mobilized from the scrotal flaps in a third stage, usually 3 to 12 months later.

Free grafts

Severe proximal hypospadias and repeat hypospadias repairs may incorporate free grafts to construct a neourethra or augment an existing plate. The versatility of most primary hypospadias repairs using preputial skin or the urethral plate, however, has obviated our need for free grafts for primary hypospadias repairs.

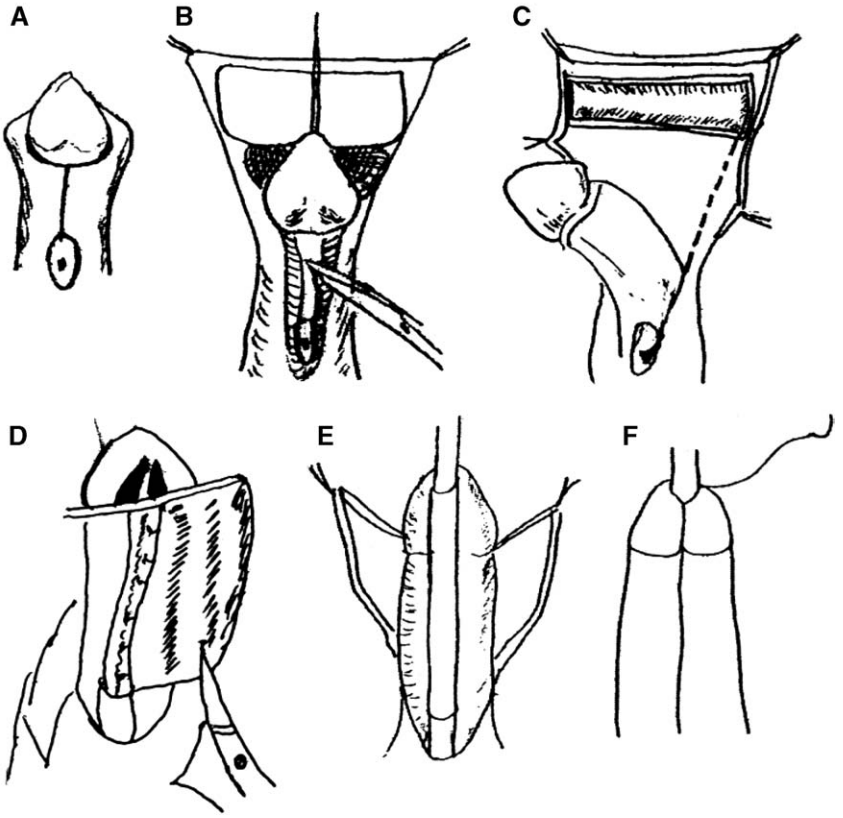

Fig. 5. Modified preputial island tube repair. (*A*) Incisions are made to facilitate degloving of the penis and circumscribe the meatus. (*B*) The urethra is opened to a point where the spongiosum is no longer divergent. The urethral plate may be transected and dissected off of the corporal tissue. (*C*) An inner preputial skin flap is harvested dorsally. The preputial flap should be harvested beginning in the middle of the pedicle and the mesentery is preserved. (*D*) The medial margin of the flap is anchored to the urethra proximally. The remaining portion of the flap is anchored to the urethral plate with interrupted, subepithelial suture. The flap further is tailored distally to roll the tube into the glans (dashed line indicates margin of urethral plate). (*E*) The glans is closed over an 8-F feeding tube. (*F*) Adequate skin coverage completes the repair with subcuticular sutures.

The authors reserve this technique for a few reoperations or the rare instances where a paucity of local tissue is evident [61]. Free skin, bladder mucosa, tunica vaginalis, and buccal mucosa have been described variously as appropriate tissue for free graft use [62–64].

In the authors' experience, bladder mucosa is less pliable than buccal mucosa. Buccal mucosa is less likely to contract. The authors usually do not oversize the graft. Buccal mucosa possesses a thicker epithelial layer than bladder mucosa and provides better tensile strength. There seem to be high levels of type IV collagen that may favor graft take [65]. Use of bladder mucosa has been abandoned in favor of the buccal mucosa in the rare cases requiring a free graft.

The authors prefer to harvest buccal mucosa from the inner cheek, taking care to avoid Stensen's duct. The graft is freed of adipose tissue and placed on a scaffold where it may be manipulated as necessary. The graft is trimmed to size if used as an onlay or tailored to be wrapped into a neourethra, without allowing for contracture in the case of buccal mucosa. The authors stent single-stage repairs completed with free grafts for 10 to 21 days depending on location and length. Recently, the authors' use of buccal mucosa has been confined to replacement of the urethral plate as a first-stage repair.

Metro and colleagues [61] and Hensle and colleagues [66] reported long-term results for buccal mucosal grafts in complex hypospadias

reoperations. Overall, complication rates from 32% to 57% were reported, with graft stricture and meatal stenosis being most common. All complications were evident by 11 months in both groups and were seen less commonly as the surgical experience widened. Buccal mucosa remains a viable nongenital tissue alternative for a select subgroup of patients requiring urethral reconstruction.

Complications

Urethrocutaneous fistula

The postoperative appearance of an urethrocutaneous fistula remains one of the most frustrating, although increasingly infrequent, complications of hypospadias surgery. Adaptations in technique, including strict adherence to the principles of plastic surgery in tissue handling, avoiding suture line overlap, and the transposition of additional tissue layers, have contributed to minimizing the incidence of failure. The team at CHOP has reported a fistula rate less than 5% for the island onlay hypospadias repair [67].

When a fistula is diagnosed, whether as a perioperative or delayed complication, at least 6 months should be allowed to elapse before repeat surgical intervention. This interval will allow inflammation and edema to resolve, and enable an accurate assessment of the viability and suitability of local tissue to be incorporated during reoperation. Although a small proximal fistula may be approached by excising the fistula tract to the urethra and performing an inverting closure with additional adjacent tissue, a larger fistula or multiple small fistulae often require a preputial or dartos-based skin flap for an onlay closure. The authors have found that smaller, distal fistulae are a deceptively more complex problem because repair often requires an onlay to ensure adequate cover as well as a reconstruction of the distal glansplasty. Transposition of considerable dorsal tissue to the ventrum with an originally completed onlay repair will provide enough tissue for a primary closure at reoperation.

Salvage hypospadias repair

Successful urethroplasty following multiple failed hypospadias repairs presents an especially difficult surgical challenge. Adherence to the surgical principles of urethrocutaneous fistula repair is requisite for success: sufficient time following failed repair, excision of the fistulous tract, closure of the urethral defect with mucosa-inverting sutures, and overlay of the urethral repair with abundantly vascularized tissue [68].

Surgeons have relied on meatal-based flaps and the tubularized incised plate urethroplasty for redo hypospadias repairs with acceptable results [69–71]. These repairs depend on the availability of adequate ventral skin or an identifiable layer of redundant dartos tissue or tunica vaginalis for additional coverage.

The authors' preference has been to complete a redo urethroplasty with an onlay island flap. The flap may be used even if the primary closure has included a dorsal pedicle. This approach rotates adequate skin for ventral penile skin coverage and provides the substrate for the construction of additional neourethra if required [72]. The authors' technique relies on redundant penile skin that is usually available along the penile dorsum. Previous reports have confirmed vascular viability and consistently favorable outcomes when previously relocated penile skin was rotated ventrally for an island onlay flap to repair hypospadias fistula [73,74].

Although Asopa and colleagues [75] introduced the concept of dual use for the preputial skin flap in their description of the double-faced preputial island flap, Gonzalez and colleagues [76] introduced the double onlay preputial flap involving ventral transposition of a total preputial island flap. The flap is positioned so that it can be divided vertically into (1) an outer flap surface that is sutured to the urethral plate to complete an onlay urethroplasty and (2) a remaining flap trimmed to cover the ventral shaft skin defect [77]. Gonzalez reported excellent cosmetic results, with a urethrocutaneous fistula rate of 17%. These patients were addressed with successful fistula closure following a single procedure in six of eight cases.

The authors call this approach the *split onlay skin (SOS)* flap for salvage hypospadias repairs. The authors use the SOS flap for salvage hypospadias repairs where urethral stenosis or multiple fistulas require a complete open urethrotomy to reconstruct a surgically damaged urethral plate, and where ventral shaft skin is deficient. The authors' technique is unique in its dual use of previously manipulated penile skin that was mobilized during the initial repair. The technique is described in Fig. 6. The SOS flap uses a transverse island of penile-shaft skin that is mobilized on its vascular pedicle and rotated into position to

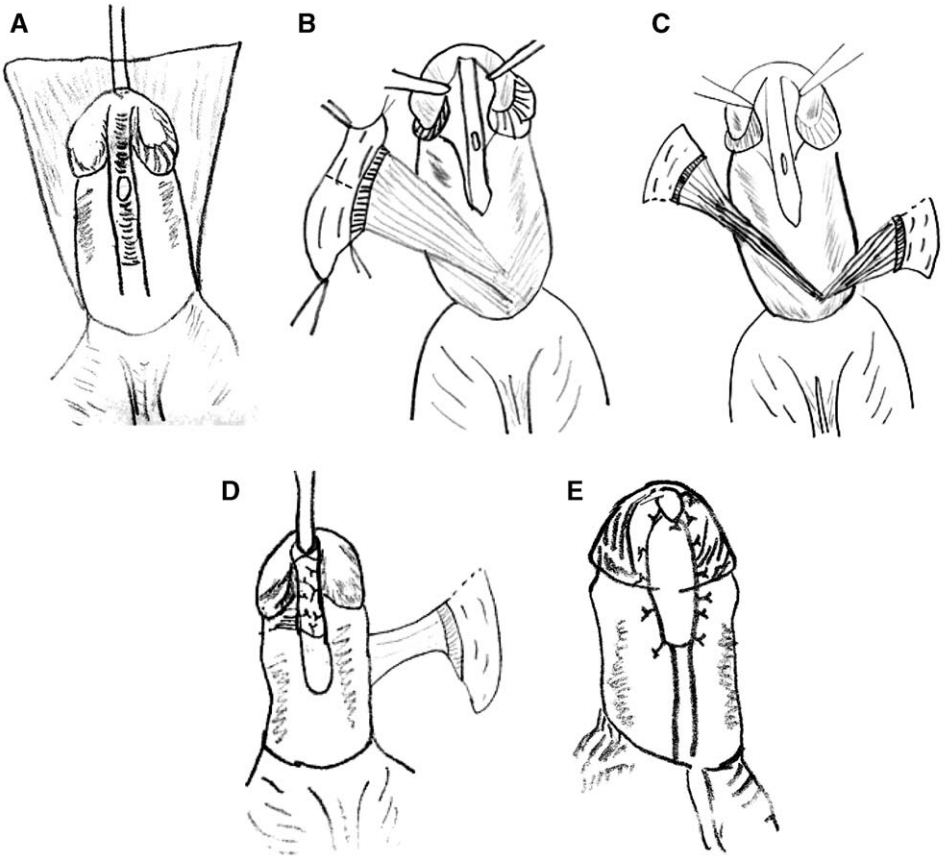

Fig. 6. Split onlay skin hypospadias repair technique. (*A*) The fistula is identified along the ventral surface of the penis following circumferential degloving of the penile skin. (*B*) An approximately 1 cm–wide dorsal preputial flap is isolated and harvested, preserving the vascular mesentery. A buttonhole is created in the mesentery and the flap is transposed ventrally. (*C*) The flap is divided transversely into two segments with the superior segment tailored to correspond to the urethral defect and to be used as an onlay flap. (*D*) The appropriately designed superior segment is sutured into place with interrupted 7-0 polyglactic sutures and a glansplasty is completed over a 6-F Kendall stent. (*E*) The residual penile skin is reapproximated dorsally and the remaining inferior segment of the rotated flap is used to cover the persistent ventral skin defect.

the ventrum of the penis at the site of the urethral defect. The flap is transected transversely; half of the flap is used as an onlay to repair the urethra and half is used for additional skin coverage where needed on the penile shaft.

This procedure was used for 11 patients with six (54.5%) boys developing postoperative fistulas. Of these, five were closed surgically with no further complications, and one penoscrotal fistula closed spontaneously after 7 months. Despite the high fistula rate following the initial SOS procedure, the authors endorse this technique because the transferred dartos tissue that would not otherwise be available facilitates the subsequent fistula repair. In this way, a complex repair is converted to a simple one. These boys can achieve a successful cosmetic result without incorporation of scrotal tissue or a free graft, which the authors believe leads to more predictable results.

Urethral diverticula and meatal stenosis

Urethral diverticula may occur as an independent complication or as a secondary consequence of meatal stenosis. Incorporating excessive tissue in a primary closure or incomplete tailoring of an onlay flap increases the likelihood of diverticula formation. The diverticulum may be trimmed followed by closure and the overlay of local tissue.

The authors prefer to wait up to 1 year to repair diverticula following an onlay or tube repair because local revascularization of the flap in that interval allows for transection of the pedicle if required at reoperation.

Urethral meatal stenosis occurs if blood supply to the distal urethra is compromised following hypospadias repair. Several technical modifications have sought to limit its occurrence. Limiting the involvement of the distal urethral plate during a TIP or MAGPI procedure and avoiding an excessively tight glansplasty are important measures to avoid meatal stenosis.

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Male neonatal circumcision: indications, controversies and complications

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Circumcision is one of the oldest surgical procedures performed today. The practice of circumcision in males and females arose in many ancient cultures. Conflicting theories have been proposed to account for this ritual, including a sacrifice or sign of submission to a deity, a fertility offering, a mark of tribal identification, a rite of passage to adulthood, and a means of humiliating and marking vanquished enemies [1]. Circumcision was performed in ancient Egypt and as a ritual by Jews and is described in Genesis [2].

Male circumcision became a common medical practice in the 19th century, with improved anesthetic, surgical, and antiseptic techniques. The prevention of masturbation was one of the primary indications for circumcision. With the "medicalization" of circumcision, such misconceptions about the role of circumcision persist [3]. Approximately one man in six is circumcised worldwide. Circumcision is the fifth most common procedure performed in the United States today [4]. In 1992, nearly 1.2 million circumcisions were performed, with 62% of newborn males undergoing the procedure [5]. The practice of circumcision the United States increased dramatically following World War II and peaked in the mid-1970s, when the American Association of Pediatrics (AAP) stated it was not a medically necessary procedure [2]. The AAP reversed its stance, however, after evidence documented an increased risk for urinary tract infections (UTIs) in uncircumcised male infants [6]. At present, routine neonatal circumcision is neither recommended nor condemned by the AAP [7]. It is left to the physician to discuss the pros and cons of circumcision, including the controversy, potential medical benefit, and complications involved with this procedure.

Controversies

Risk for urinary tract infection

Uncircumcised infant males are at increased risk for UTI, especially during the first year of life [6,8–14]. The increase in risk is presumably secondary to increased periurethral bacterial colonization. The incidence of UTI in uncircumcised males is low and ranges between 1 in 100 and 1 in 140. UTI risk seems to be reduced in circumcised males by up to 10 fold. Many of the studies examining the role of circumcision in preventing UTI have not assessed and controlled systematically for other factors, including breastfeeding, that may decrease risk. A recent study has suggested that tight covering of the urethral meatus by the prepuce may increase the risk for UTI [15]. The low risk for UTI in uncircumcised males does not warrant mandatory circumcision. See later discussion for the role of circumcision in those at higher risk for UTI.

Anesthesia/analgesia

Neonatal circumcisions usually are performed within the first several days of life. Before the 1990s, anesthesia was not used routinely. In a recent survey of physicians stratified by specialty and geography, 35% of pediatricians, 60% of family practitioners, and 70% of obstetricians responding to a questionnaire performed at least one circumcision per month. Of these physicians, only 45%

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reported using anesthesia for the procedure. Pediatricians were more likely to use anesthesia (71%) than family practitioners (56%) or obstetricians (25%). Recent training was a factor in anesthetic use in primary care doctors but not in obstetricians. The most common reasons cited for not using anesthesia were concern over adverse reactions and the opinion that the procedure does not warrant anesthesia [5].

There is no question that newborn infants exhibit responses to pain, whether measured by physiologic or behavioral means [16]. Behavioral and physiologic differences have been demonstrated in neonate boys undergoing circumcision as measured by increased heart rate, prolonged crying, and decreases in oxygen tension. These responses are ameliorated by the injection of local anesthesia [17].

Several methods of pain control have been described [18]. Eutectic mixture of local anesthetics (EMLA cream) decreases crying interval and cardiac response to neonatal circumcision compared with placebo [19–21]. This technique may be limited in its efficacy during maximum trauma and carries the risk for inducing methemoglobinemia when used in quantities greater than 1 g. EMLA cream should not be used in conjunction with other drugs that can induce methemoglobinemia, including sulfa drugs [22,23].

Dorsal penile nerve block using 1% lidocaine reduced pain during neonatal circumcision in controlled trials. The most frequent complication of this procedure is bruising, with hematomas occurring rarely. The potential for systemic absorption may be limited by aspirating before injecting and injecting at the 10-o'clock and 2-o'clock positions rather than in the midline [24,25]. Circumferential injection of 1% lidocaine at the midshaft of the penis (ring block) may be more effective than dorsal nerve block and EMLA cream at ameliorating pain with circumcision [22].

Allowing the infant to suck on a cloth soaked with sweet wine often is used in religious circumcisions. This technique may reduce the stress and trauma of the procedure, as evidenced in a study comparing sucrose on a pacifier versus water. Such "comfort" measures may reduce pain, but are not a substitute for anesthetic methods [26].

Sexual function

The function of the prepuce in human sexual response continues to be debated. Many groups object vehemently to the practice of circumcision because they believe the procedure is a form of mutilation and permanently inhibits sexual function.

To consider whether removal of the foreskin may alter sexual function negatively, one must first consider the function of the prepuce. The prepuce is a specialized mucosal surface lined by squamous epithelium similar to mucosa of the mouth, vagina, and esophagus. It is rich in nerves with multiple Meissner's corpuscles that are similar to nerve endings in the fingertips and lips [27]. During sexual intercourse the foreskin is thought to provide a gliding mechanism for the penis during thrusting and may prevent the loss of vaginal secretions [28].

Circumcision removes the protective barrier of the glans penis, resulting in increased keritinization of the glans. Removal of the prepuce effectively stops the production of *smegma*, the exudate of dead skin cells and oils that may have pheromonic properties [29]. Masters and Johnson [30] found no differences in glanular tactile sensation in circumcised men. They did not study, however, alterations in fine touch that may be affected by circumcision. The glans is insensitive to light touch, heat, and cold and is a primitive sensory organ. Thus, characterization of glans sensation pre- and postcircumcision may not delineate true alterations in sensation associated with removal of the prepuce [27].

In a recent survey of men undergoing circumcision, a significant number of patients noted worsened erectile function and decreased penile sensitivity, but noted improved satisfaction. These seemingly conflicting outcomes may be explained by the hypothesis that curing the underlying problem (phimosis in 64% and recurrent balanitis in 17%) was of greater importance to most patients responding to the survey [31]. Contrary results, however, were found in a prospective sexual function survey of men before and 12 weeks after circumcision. There was no statistically significant difference in reported sexual drive, erection, ejaculation, or overall satisfaction. This study had limitations, however; the study population was composed of men undergoing circumcision for medical conditions of the prepuce, and thus their perceptions of function may have been altered [32].

Laumann and colleauges [33] used the National Health and Social Life Survey (NHSLS) to compare rates of sexually transmitted diseases (STDs), sexual dysfunction, and sexual practices. Although no differences were found in rates of the former

two categories, circumcised men were more likely to engage in elaborate sexual practices, including masturbation and anal intercourse. Removal of the prepuce may alter sensation, resulting in the individual seeking alternative forms of stimulation. The latter study is especially intriguing because circumcision was performed in the 19th century to prevent masturbation [3].

One should consider the potential effects of male circumcision on the female partner. O'Hara and O'Hara [34] surveyed women having sexual experience with circumcised and uncircumcised partners. The women were recruited by classified advertisements in magazines, including an anticircumcision newsletter. Fewer than half (49%) of the surveys mailed to respondents to the advertisements were returned. A significant number of women noted greater likelihood of experiencing vaginal orgasm, less discomfort, and greater intimacy with an uncircumcised partner. Although this study had methodologic flaws, it underscores the need to consider the female partner when investigating sexual function outcomes postcircumcision.

Circumcision and malignancy

Circumcision during infancy seems to decrease risk for penile cancer, whereas later circumcision does not [35]. Squamous-cell carcinoma of the penis is rare in circumcised men. Rates of penile cancer vary in uncircumcised men, depending on many variables, including geographic location, presence of phimosis, number of sexual partners, and cigarette smoking. Although the risk for developing penile cancer may be higher in uncircumcised men versus circumcised men, the overall incidence is low in developed countries, perhaps demonstrating that hygienic measures may play a key role in preventing the development of cancer [7,36–42].

Circumcision and sexually transmitted diseases

Prevention of STDs has been a commonly cited indication for circumcision since the procedure became "medicalized" [3]. A report that Jewish men had lower rates of syphilis fueled this theory in the 19th century [43,44].

In Van Howe's [44] recent review of the literature, only 31 studies with identifiable controls were found and analyzed. This review found no clear evidence that circumcision prevents STDs. If one considers syphilis alone, there are many conflicting studies regarding the role of the prepuce in disease risk [33,45,46]. Uncircumcised men may be at increased risk for infection with HIV, but several studies have shown circumcised men to be at higher risk, and others show no effect of circumcision status [47–50]. Such conflicting studies yield the conclusion that circumcision as a routine procedure cannot be justified as a means of preventing STDs.

Indications and contraindications

Contraindications

Circumcision generally is not performed in premature infants. It should not be performed in children with congenital anomalies of the penis, including hypospadias, epispadias, chordee, penile webbing, and concealed penis. Any child with blood dyscrasias should not undergo circumcision.

Indications

The medical indications for circumcision remain controversial. The religious beliefs of the parents must be respected when considering circumcision [51–53].

Phimosis

Phimosis is the most common diagnostic code used in conjunction with circumcision [54]. A basic understanding of the embryology/physiology of the prepuce is important in understanding what is a pathologic state of the penis. Preputial development begins at 8 weeks gestation and is complete by 16 weeks, when the mucosa of the prepuce and glans are contiguous. The process of desquamation or exfoliation of the underlying epithelial tissue pushes the two surfaces apart, resulting in lysis of the physiologic adhesions and resolution of the physiologic "phimosis." This process happens gradually and is usually complete by 3 years of age, although it may persist until the age of sexual maturity. Thus, this type of phimosis is not a disease or medical condition, but is a natural process and not an indication for circumcision [54–57].

True or pathologic phimosis is far less common and is associated with white, cicatrical, scarred tissue present at the preputial ring. The symptoms include irritation of the skin, dysuria, bleeding, and occasionally urinary retention and enuresis. Although circumcision is curative, alternative treatments, including preputioplasty (dorsal slit) or the

application of steroid creams, should be considered [54,57].

Urinary tract infection

Although UTIs are more likely to occur in uncircumcised males younger than 6 months of age, the overall incidence of UTI in this age group is low [10,11]. After 6 months of age, the association is not seen, likely because of the resolution of physiologic adhesions/phimosis. Circumcision should be discussed with parents of infants in whom UTI would pose an increased risk for renal injury, including infants with vesicoureteral reflux, obstructing hydronephrosis, and posterior urethral valves and other congenital anomalies. The use of prophylactic antibiotics or alternatives to circumcision as discussed above, however, should be considered.

A multicenter study examined patients with vesicoureteral reflux and a prenatal history of hydronephrosis [58]. The authors noted a statistically significant difference in 63% of the uncircumcised boys with reflux and UTIs compared with 19% of the circumcised boys, despite each group being on antibiotic prophylaxis. This finding suggests that removal of the prepuce may protect against UTIs in boys with reflux.

Complications

Circumcision is a safe surgical procedure that is well tolerated in nearly all patients. There are known risks attendant to the procedure, however, that should be discussed with the patient's parents to ensure that informed consent is obtained. The incidence of complications varies between 0.2% to 3% [2,57].

Death

Death from circumcision is rare, but has been described in the literature. Recently, the death of a 5-week-old boy from bleeding-related complications was reported [59]. During one period in New York City, however, no fatalities were reported in 500,000 consecutive neonates undergoing circumcision [60].

Bleeding

Bleeding is the most common complication of circumcision [2]. A common site of bleeding is from the vessels of the dorsal dartos fascia that may be in spasm at the conclusion of the procedure and then begin to ooze. Most bleeding can be controlled with direct pressure or application of silver nitrate to an obvious bleeding vessel. Occasionally it is necessary to explore the wound, especially if a hematoma is present or the vessel is deep within it. One should consider hematologic evaluation of the patient if the bleeding is persistent or significant. The use of a dressing has not affected complication rates of other penile surgery and likely does not matter in circumcision [61].

Suture sinus tracts

Suture sinus tracts occur when a simple suture becomes epithelialized before absorption of the suture material. A skin bridge is formed that may collect dirt and bacteria, thus presenting a hygienic issue. Suture sinus tracts frequently are unnoticed by the patient, and their true risk to the patient is uncertain. They may be excised if associated with recurrent infections or poor hygiene.

Infection

Infection is an infrequent complication of circumcision despite the infant penis's dirty environment. The excellent blood flow to the penis likely explains the low infection rates. Infecting organisms are typically skin flora, but prophylactic antibiotics are not used typically in pediatric circumcision. Good postoperative care of the wound is important to prevent complications, including infection [57]. Parents often fear touching the penis postcircumcision because of anxiety about hurting their child. It is important to reassure them that the penis should be cleaned regularly at diaper changes. The author prescribes an antibiotic ointment to be applied at diaper changes.

Phimosis and concealed penis

Phimosis may occur after circumcision for several reasons. Typically, there is redundant inner preputial skin that may slide back over the glans, resulting in cicatrical contraction of the incision and trapping of the penis. If there is abundant suprapubic fat and the dartos attachments to the skin are loose, the penis may become buried or concealed. The surgeon performing circumcision should take care to ensure that the adhesions of the prepuce to the glans are taken down completely. Occasionally there is a discrepancy between too much dorsal skin and too little ventral skin. If standard circumcision is performed, the penis may become buried. The pediatric urologist should have command of the many different techniques

to treat penile concealment because each situation can be different, requiring a different approach [62].

Adhesions

Adhesions occurring after circumcision can be divided into two forms: surgical and nonsurgical (or congenital). At birth, most uncircumcised males have adhesions of the inner preputial skin to the glans as discussed above. The adhesions gradually resolve as the underlying skin exfoliates, creating smegma, a white exudate of dead skin cells and keratin that often is misdiagnosed by parents and pediatricians as an infection. The smegma often seems to be a pearl-like ball of tissue that is extruded from beneath the adhesion. Parents should be reassured that this is a natural process and not infectious.

Surgical adhesions may occur as the circumferential incision heals to the glans. During this healing process, a skin bridge may form between the circumcision incision and the glans [2,57]. These skin bridges typically occur on the dorsal surface, but may surround the penis completely. The skin bridges at first are almost transparent in infants. As the child ages, the skin bridge thickens. Skin bridges present a hygienic issue because dirt may collect beneath them. Although usually simple to excise, if they are circumferential and have persisted for years, excision may be challenging. In this case, parents should be counseled as to potential deformity or scarring of the glans post-procedure.

Meatitis

Erythema of the meatus is a common finding postcircumcision, but usually resolves as the epithelial surface thickens in response to the irritation. This erythema typically does not cause symptoms, although some older children complain of pain and dysuria. Parents should be reassured as to the self-limiting nature of the erythema [2].

Meatal stenosis

Narrowing of the meatus likely occurs in response to chronic irritation of the meatus and it typically does not occur in circumcised males. Some theorize that it occurs secondary to ligation of the frenular artery after circumcision. Meatal stenosis does not require treatment unless the stream is deflected or, rarely, if it is associated with dribbling of urine, dysuria, or urinary frequency [2,57]. The author has been referred many patients who had persistent voiding symptoms despite adequate meatotomy. The urologist should not underestimate the ability of the meatus to expand during micturition. As urine flows into the fossa navicularis, force is imparted circumferentially on the glanular urethra and meatus, creating a wider opening.

Chordee

True chordee of the corporal bodies is not a complication of circumcision. Curvature of the penis, however, may occur after circumcision if an uneven amount of skin is removed. Attention to the anatomy of the penile shaft skin during circumcision can help prevent this problem [2].

Urethrocutaneous fistula

Urethrocutaneous fistula is a rare complication of circumcision. Although fistulas may be congenital, one may occur if the urethra is injured during circumcision. Such injury may occur during excision of the prepuce or during wound closure [2].

Necrosis

Necrosis of the glans and corporal bodies is a rare but devastating complication of circumcision that may result from infection or from surgical complications. As a rule, the author does not use electrocautery on the penis, and uses bipolar cautery instead. Use of electrocautery in conjunction with a clamp device is a dangerous maneuver and has resulted in complete loss of the penis (W.H. Hendren, personal communication).

Amputation

Avulsion and true partial-amputation of the glans may occur, typically when a circumcision is performed using a clamp. If the injury is recognized in a timely fashion, the amputated tissue should be placed in a sponge dampened with normal saline and transported on ice with the patient. Necrotic tissue should be debrided before reattachment is attempted [2].

Hypospadias

A circumcision may cause hypospadias if the clamp is misplaced and the ventral glans is avulsed [2].

Summary

The debate about whether to circumcise infants in the neonatal period likely will continue for some

time. As the medical and ethical issues are discussed and studied, however, economic factors are beginning to limit the practice in the United States. For example, Medicaid no longer funds neonatal circumcision in 11 states [63]. Private insurers likely will follow the lead of state health insurance, and a decline in the rate of circumcision will follow. As this shift in reimbursement occurs, parents who believe that circumcision is a medically necessary practice will need to be reassured that their child may lead a healthy life with an intact foreskin.

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Cryptorchidism: diagnosis, treatment, and long-term prognosis

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Cryptorchidism or an undescended testis is the most common disorder of the male endocrine glands in children. One third of boys with true cryptorchidism have bilaterally cryptorchid testes, whereas two thirds of boys have a unilateral cryptorchid testis [1–3]. The main reasons advocated for the treatment of cryptorchidism are increased infertility in patients with unilateral and bilateral cryptorchid testes, an increased testicular malignancy rate, an increased risk for testicular torsion or injury against the pubic bone, and the psychologic stigma of an empty scrotum. The current standard of therapy in the United States is surgical repositioning of the testis within the scrotal sac (orchiopexy), whereas hormonal manipulation is more widely used in Europe. Despite successful relocation of the testis, long-term sequelae of cryptorchidism occur, including infertility, subfertility, and malignancy.

Epidemiology

The incidence of cryptorchidism ranges between 3.4% and 5.8% in full-term boys and has been reported to be as high as 30% in premature boys [1–3]. The prevalence decreases to approximately 0.8% at about 1 year of age and remains at this level essentially throughout adulthood. A small increase in the prevalence in prepubertal boys has been reported by several investigators. This increase may be due to observer error in patients with retractile testes [2,4–6]. It has been theorized that spontaneous descent in infancy may occur owing to the normal gonadotropin surge that occurs around 60 to 90 days of life [7–10]. Gendrel et al and Job et al reported blunting of this surge in boys in whom the testes remained undescended in the first year of life [7,8]. They demonstrated a significant difference in the polynomial regression curves comparing the testosterone levels of persistently cryptorchid testes with those having delayed spontaneous descent. Nevertheless, the positive predictive value that bilateral undescended testes will have abnormally low testosterone levels is only about 23% [7]. Other studies have not found a significant reduction in the testosterone levels when comparing patients with undescended testes with controls [11]. Advanced maternal age, maternal obesity, a family history of cryptorchidism, preterm birth, and consumption of cola-containing drinks during pregnancy have all been suggested as possible risk factors for cryptorchidism [12].

Etiology

Despite the relatively frequent incidence of cryptorchidism, the etiology and molecular markers of future fertility or malignancy remain obscure [13]. Cryptorchidism is a well-known manifestation of chromosomal abnormalities and a common component of more than 50 syndromes of multiple congenital anomalies [14]. When associated with other congenital anomalies like hypospadias, cryptorchidism has a higher incidence of chromosomal anomalies (12% to 25%) than when it occurs unaccompanied (3% to 4%) [15–18]. No consistent chromosomal disorder is associated

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with isolated cryptorchidism. Several case series of the familial occurrence of cryptorchidism have demonstrated that a heritable component exists [19–23]. Furthermore, large epidemiologic studies have shown a consistent pattern of inheritance for isolated cryptorchidism. Of boys with undescended testes, 4.0% of their fathers and 6.2% to 9.8% of their brothers also had undescended testes [2,3,24]. Elert et al [25] conducted a study to examine the frequency of a positive family history and to calculate the risk for the newborn males of an undescended testis. They concluded an overall risk of 3.6-fold over that for the general population if a family member was affected. This familial incidence exceeds the 1% to 3% incidence of cryptorchidism in the general population [1]. These inheritance patterns are consistent with a multifactorial etiology of cryptorchidism.

Androgen influence

Hutson has proposed that testicular descent occurs in two phases. The initial transabdominal aspect may be controlled by müllerian inhibiting substance (MIS) [26]. The inguinoscrotal descent seems to be androgen dependent and is mediated indirectly through the release of calcitonin gene-related peptide (CGRP). Androgens act on the genitofemoral nerve, which is sexually dimorphic and releases CGRP upon stimulation, producing rhythmic contractions of the murine gubernaculum. Hutson et al found that two rodent models of cryptorchidism had deficiencies of CGRP in the genitofemoral nerve (the tfem mouse and the rat prenatally exposed to antiandrogen).

Inguinoscrotal descent is blocked in mice with complete androgen resistance (testicular feminization) in which the androgen receptor gene (*AR*) has been knocked out [26,27]. Deletions and mutations may cause structural changes in the androgen receptor, altering its function [28]. As much as 50% to 70% of male pseudohermaphroditism, which includes hypospadias and cryptorchidism, is caused by *AR* gene disorders (androgen insensitivity syndrome [AIS]), suggesting a role for androgens in this developmental process [29,30]. Most *AR* gene mutations identified are in the DNA-binding (exons 2-3) and ligand-binding (exons 5-8) domains; however, the same mutation can result in a different or even a normal phenotype in members of the same family [31,32]. Phenotypic variations in families affected by partial AIS are thought to be modulated by factors other than, or in addition to, point mutations of the *AR* gene. Furthermore, the role of the *AR* gene mutations in isolated forms of hypospadias or cryptorchidism is unclear. They are a definite yet uncommon cause of hypospadias but have not yet been identified in isolated cryptorchidism [18, 33–35].

Exon 1 of the *AR* gene contains the transactivation domain and encodes polymorphic glutamine (CAG) repetitive sequences. The CAG repeat length ranges from about 15 to 30 units in controls, exhibiting ethnic variability [36]. Within this spectrum, the CAG length influences androgen receptor function, providing enhanced androgen action with a shorter repeat length and decreased function with a longer length [37]. Mutations in a series of cytosine-adenosine-guanine (CAG) trinucleotide repeat sequences located at a polymorphic region in exon 1 of the *AR* gene have been linked to an X-linked neuromuscular disease termed *spinal bulbar muscular atrophy* or Kennedy's disease [38]. Affected men display subtle signs of androgen resistance, such as gynecomastia, testicular atrophy, and reduced fertility. Increased *AR* CAG length has also been related to male infertility through defective spermatogenesis, although others have found conflicting results [39–41]. Within the normal polymorphic range, an expansion of the CAG tract decreases the androgen receptor activity and may be associated with cryptorchidism or infertility. The authors have seen an increased CAG length when both cryptorchidism and hypospadias were present [21]. Ogata et al [42,43] reported an abnormally expanded CAG length in a boy with undermasculinized genitalia, but later concluded that CAG expansion is not likely a major cause of cryptorchidism.

INSL3/GREAT genes

Several investigators have examined the role of the Leydig insulin-like hormone gene (*INSL3*) as a putative trophic hormone of the first part of testicular descent. It is a member of the insulin hormone superfamily and is expressed in the developing testis. Mice mutant for *Insl3* are viable but exhibit bilateral cryptorchidism [20,44,45]. These mice have developmental abnormalities of the gubernaculum and abnormal spermatogenesis and infertility. Nevertheless, in a manner similar to the *AR* gene, mutations of the *INSL3* gene in humans are infrequent [46–48]. The *GREAT* gene is also highly expressed in the gubernaculum. Mutations in this gene have been associated with

cryptorchidism in the mouse and, rarely, in humans [49,50]. Recently, the ligand for the *GREAT* gene has been identified as the *INSL3* peptide [51–53]. In some patients, an abnormal gubernaculum may have a role in testicular descent. These previously identified genes may work in concert to help control testis development and migration.

Homeobox genes

Homeobox (*HOX*) genes have a key role in the morphogenesis of segmental structures along the anteroposterior body axis [54]. These genes act as master regulatory switches or transcription factors that specify axial identity and control the growth and differentiation of cells related by position. Murine *hox a10* knockout male mice exhibit bilateral cryptorchidism with developmental abnormalities of the gubernaculum and resultant abnormal spermatogenesis and infertility [55,56]. Similarly, mice homozygous for *hox a11* deletions are also infertile and cryptorchid [22,57]. Many other gene products have been targeted as being expressed in testicular differentiation (ie, *PAX5, SRY, SOX9, DAX1, MIS*) but not specifically in cryptorchidism [58,59].

Other factors

Endocrine disruptors have been hypothesized to have a role, because androgens contribute significantly in the pathophysiology of spermatogenesis and testicular descent. Diethylstilbestrol (DES) is by far the best known and studied chemical for its antiandrogenic effects. Boys exposed to DES in utero have an increased number of genital abnormalities including cryptorchidism [60]. This observation further advocates a multifactorial and complex etiology of cryptorchidism.

Secondary cryptorchidism can occur after inguinal surgery, owing to scar tissue or difficulty in diagnosing an undescended testis in a young boy with a hernia. An ascending testis is one that appeared descended at birth and later ascended. Reports suggest that an ascending testis has similar histology on testis biopsy to an undescended testis [61]. Yearly examination should be performed in questionable cases to identify a true undescended testis.

Gonadal development

During the first 3 to 5 weeks of gestation, the gonads are undifferentiated. By the sixth week, the primordial cell migration from the wall of the embryonic yolk sac along the dorsal mesentery of the hindgut to the genital ridge is completed [62]. By the seventh week, the bipotential gonad is differentiated into the fetal testis under the influence of the SRY protein, which, in turn, is regulated by the *SRY* gene located on the short arm of the Y chromosome [63]. Between the seventh and ninth week, Sertoli cells secreting MIS and Leydig cells secreting testosterone develop [64,65]. MIS causes regression of müllerian structures, and testosterone causes development of the wolffian duct to form the epididymis and vas deferens [66,67]. External genitalia develop between the eighth and sixteenth week. Canalization of the rete testis and mesonephric tubules begins in week 12 and is completed by puberty. Testicular descent occurs in the seventh month of gestation and depends on multiple factors discussed earlier.

Undescended testis histology

Primordial germ cells differentiate into gonocytes by entering the testicular cords. Some gonocytes attach to the basement membrane and give rise to fetal spermatogonia, which then transform into type A spermatogonia (first Adult dark [Ad], then Adult pale [Ap]) during the third to fifth months of life (Fig. 1). The B spermatogonia and the primary spermatocyte appear during the fourth year, and spermatogenesis arrests at this stage until puberty. In the cryptorchid testis, the number of Leydig cells is decreased, and they appear atrophic. In the first 6 months of life, the total number of germ cells is within the normal range in cryptorchid testes; however, the number of spermatogonia remains low and does not increase with age (Fig. 2). These findings support the lack of transformation of gonocytes into spermatogonia in the cryptorchid testis. The normal postnatal development of Leydig cells and germ cell transformation parallel the normal gonadotropin and resultant testosterone surge around 60 to 90 days of life [68].

Diagnosis

History and physical examination

A thorough history should note any prematurity (the incidence of undescended testes in premature boys is as high as 30%), maternal use or exposure to exogenous hormones (estrogens), lesions of the central nervous system (myelomeningocele), or previous inguinal surgery. One

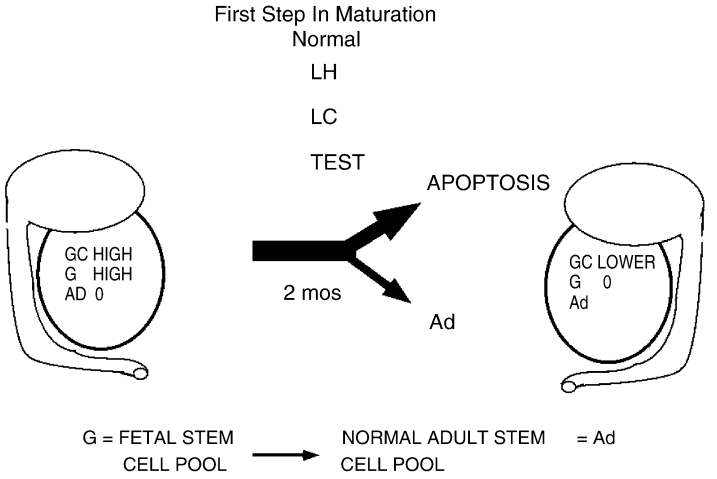

Fig. 1. Differentiation of gonocytes into Ad spermatogonia. G, gonocyte; GC, germ cell; LC, Leydig cell; LH, luteinizing hormone; TEST, testosterone.

should document a family history of cryptorchidism and other congenital anomalies, neonatal deaths, precocious puberty, infertility, and consanguinity. It is should be determined whether the testes were ever palpable in the scrotum at the time of birth or within the first year of life. Testicular retraction owing to a strong cremasteric reflex is most apparent between 4 and 6 years of age and may lead to an inaccurate diagnosis of undescended testes [68].

An undescended testis can be classified by its location in the upper scrotum, in the superficial inguinal pouch, in the inguinal canal, or in the abdomen. For treatment purposes, the main distinction that needs to be made is whether the testis is palpable.

The patient should be examined supine in the frog leg position with both legs free. With warmed hands, the examiner should check the size, location, and texture of the contralateral descended testis. Examination of the undescended testes should be started at the anterosuperior iliac spine, sweeping the groin from lateral to medial with the nondominant hand. Once the testis is palpated, the examiner should grasp it with the dominant hand and continue to sweep the testis toward the scrotum with the other hand. With a combination of sweeping and pulling, it is sometimes possible to

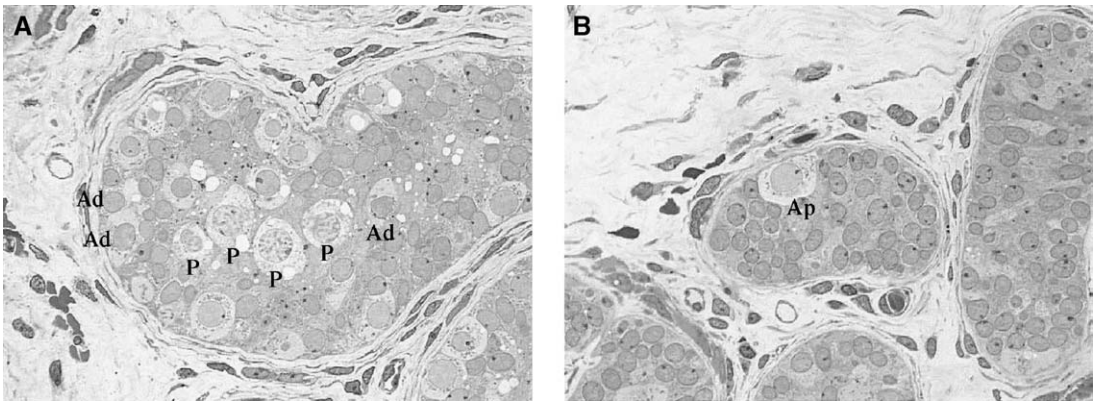

Fig. 2. (*A*) Descended testis biopsy showing Adult dark (Ad) spermatogonia and primary spermatocytes (P). (*B*) Cryptorchid testis biopsy showing paucity of Ad spermatogonia and persistence of fetal gonocytes with an Adult pale (Ap) spermatogonia.

bring the testis to the scrotum. The position of the testis in the scrotum should be maintained for a minute so that the cremaster muscle is fatigued. One can then release the testis. If it remains in place, it is a retractile testis; if it immediately pops back, it is an undescended testis.

For the difficult-to-examine patient (chubby 6-month-olds or obese youths), the sitting cross-legged position or the "baseball catcher's position" can help relax the cremaster muscle. Wetting the fingers of the nondominant hand with lubricating jelly or soap can increase the sensitivity of the fingers in palpating the small mobile testis.

A retractile testis is often confused with an undescended testis. The key to distinguishing a retractile testis from an undescended testis is demonstrating that the testis can be delivered into the scrotum. The retractile testis will stay in the scrotum after the cremaster muscle has been overstretched, whereas the low undescended testis will immediately pop back to its undescended position after being released. If there is any question, the child should be seen in follow-up for a repeat examination.

An atrophic or vanishing testis can be found anywhere along the normal path to the scrotum. The etiology is thought to be neonatal vascular ischemia, possibly owing to torsion [69]. The contralateral descended testis may be hypertrophied in these boys, but this is not a reliable diagnostic sign.

At evaluation, 80% of nonpalpable testes are present in the inguinal canal or in an intra-abdominal location. The presence of bilateral undescended testes should raise suspicion of an endocrine disorder or an intersex state that should be evaluated. Cryptorchidism associated with hypospadias, especially proximal, should also raise the possibility of an intersex state. This condition occurs in 30% to 40% of the patients, mainly consisting of defects in the testosterone synthesis pathway [70].

Laboratory tests

In boys with unilateral or bilateral undescended testes in whom one testis is palpable, no further laboratory evaluation is necessary to aid the diagnosis [71]. In boys with bilateral undescended testes in whom neither testis is palpable and in boys with associated hypospadias, chromosomal and endocrinologic evaluation may be performed but is not always necessary [16]. In patients 3 months of age or younger with bilateral nonpalpable undescended testes, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone levels will help determine whether the testes are present. After 3 months of age, a human chorionic gonadotropin hormone (hCG) stimulation test will aid in the diagnosis of the absent testes. A failure to see a measurable testosterone level in combination with elevated LH/FSH is consistent with the diagnosis of anorchia [72,73].

Imaging

Ultrasound, CT, and MR imaging can detect testes in the inguinal region, but this region is also where they are easily palpable. The accuracy of ultrasound and CT in showing intra-abdominal testes falls to 0% to 50% in various series [71]. Hrebinko and Bellinger found that the most reliable mode of evaluation was physical examination by a pediatric urologist (84%) when compared with examination by a referring physician (53%) [71]. The accuracy of the radiologic examination was 44%, and the study did not influence the management decision in any of the cases. Yeung et al [74] employed gadolinium-enhanced MR angiography to identify 100% of canalicular undescended testes and 96% of intra-abdominal undescended testes (one missed vanishing testis). Although this technique is expensive and requires sedation, it may prove to be the best diagnostic tool. Currently, for patients with nonpalpable testes, examination under anesthesia, open inguinal exploration, or laparoscopy is necessary to confirm the presence of testes.

Treatment

Hormonal therapy

Primary hormonal therapy with hCG or gonadotropin-releasing hormone (GnRH) or LH-releasing hormone (LHRH) has been used for many years, especially in Europe. The action of hCG is virtually identical to that of pituitary LH, although hCG seems to have a small degree of FSH activity as well. It stimulates the production of gonadal steroid hormones by stimulating the Leydig cells to produce androgens. The exact mechanism of action of the increased androgens in testicular descent is not known but may involve effects on the testicular cord or cremaster muscle. This medication is administered by intramuscular injection. Multiple series have been published. Owing to differences in patient age, treatment

schedules, and the possible inclusion of retractile testes, divergent results have reported.

Many dosage schedules are reported, ranging from 3 to 15 doses [75–77]; however, hCG seems to be as effective in three or four doses versus nine or ten doses. One of the most common schedules is 250 IU/dose in young infants, 500 IU/dose in patients up to 6 years old, and 1000 IU/dose in patients aged more than 6 years given twice a week for 5 weeks (International Health Foundation). Success rates for descent into the scrotum are 25% to 55% in uncontrolled studies versus 6% to 21% in randomized blinded studies. Distal inguinal testes in older boys are more likely to descend in response to hormonal treatment than are abdominal testes. Repeated courses have offered little advantage. Side effects of hCG treatment include increased scrotal rugae, pigmentation, pubic hair, and penile growth that regresses after treatment cessation. A total dose of more than 15,000 IU may induce epiphyseal plate fusion and retard future somatic growth.

Agonistic analogues of GnRH, such as nafarelin or buserelin, stimulate release of the pituitary gonadotropins LH and FSH, resulting in a temporary increase of gonadal steroidogenesis. Repeated dosing abolishes the stimulatory effect on the pituitary gland, and twice daily administration leads to decreased secretion of gonadal steroids by 4 weeks. This hormone is available as a nasal spray but is only approved in Europe for the treatment of cryptorchidism. Interpretation of the results is tainted by multiple treatment strategies. Success rates in uncontrolled studies range from 13% to 78%, whereas the rates in better-controlled investigations range from 6% to 38% [78,79]. Rajfer et al conducted a randomized, double-blind study comparing hCG, 3300 IU per week for 4 weeks, with GnRH spray, 200 μg six times a day for 4 weeks. Descent into the scrotum occurred in 6% of the hCG group and 19% of the GnRH group [77]. Several investigators have recommended combined GnRH-hCG hormonal treatment. Lala et al [79] administered LHRH, 1.2 mg/day for 4 weeks; nonresponders also received hCG, 500 IU three times a week for 3 weeks. After combined treatment, 38% of the testes descended. Bica and Hadziselimovic [80] treated patients with a low dose of buserelin, 20 μg as a daily spray for 28 days, followed by hCG for failures. Twenty-six percent of the testes descended with the spray alone, and hCG increased the descent rate to 37%. Hadziselimovic et al [81] advocated initial treatment with GnRH spray, 400 μg three times daily into each nostril for 4 weeks, followed by salvage treatment for failures with hCG, 1500 IU/week for 3 weeks. A success rate of 56% with GnRH was increased to 65% with the addition of hCG.

The recognized side effects of increased androgens, including increased penile or testicular size, scrotal erythema, or erections, seem to be less with GnRH than with hCG. Initial treatment with GnRH may deserve some consideration, because it is administered as a spray rather than an injection. In 20% of patients, it may aid descent in more distal testes, make intra-abdominal testes palpable, or help differentiate retractile from true undescended testes. Hormonal therapy may also have prophylactic value [82]. Use of LHRH analogue in boys with severe histologic changes in the testis (total germ cell count less than 0.2 germ cells/tubule in undescended testes and less than 0.6 germ cells/tubule in the contralateral descended testis) has an advantageous effect on the developing germ cells. In a study by Huff et al [83], patients who had no germ cell count on the biopsy did not show improvement after hormonal therapy, whereas those who had some germ cells demonstrated improvement. This improvement in germ cell count and maturation may eventually reflect a better prognosis for fertility. Hadziselimovic and Herzog [84] showed that boys who were treated with hormones had better semen analyses when compared with boys who had orchiopexy alone or placebo treatment.

Surgical treatment

The child is placed supine in the frog leg position. Re-examination is performed under anesthesia, because a previously nonpalpable testis may become palpable, circumventing abdominal exploration. Gatti et al [85] have recommended performing a digital rectal examination under anesthesia before surgery. In their hands, overall specificity of the digital rectal examination has been 100%, but the sensitivity is only 60%.

Palpable testis

The surgical technique involves the following steps:

An incision is made over the inguinal canal along Langer's lines.

Care is taken when incising Scarpa's fascia, because the testis may be located in the

superficial inguinal pouch and not in the inguinal canal.

Division of the distal gubernacular attachments is performed.

Transection of the cremasteric muscle fibers is performed.

The cord structures are separated from the peritoneum above the internal inguinal ring during ligation of the hernia sac.

Division of the lateral spermatic fascia is performed to allow medial movement of the testis.

Isolation and high ligation of the patent processus vaginalis on the anteromedial surface of the cord is completed.

The testis is relocated into the scrotum in a subcutaneous or subdartos pouch.

The following additional maneuvers may be employed for adequate length of an inguinal testis:

- In the Prentiss maneuver, the surgeon divides (or passes the testis under) the inferior epigastric artery and vein and opens the transversalis fascial layer.
- The internal inguinal ring may be opened by dividing the internal oblique muscles and more of the lateral spermatic fascia. The inguinal incision may also be lengthened to enable this dissection. Dissection is then continued in the retroperitoneal space.
- Fowler-Stephens orchiopexy with division of the internal spermatic artery may be performed, allowing the testis to survive on the blood supply of the vas deferens and the cremasteric attachments. This maneuver may be employed only when extensive dissection of the vas and cord has not already occurred. The region of transection of the spermatic artery is controversial. Fowler and Stephens [86] originally reviewed the vascular anatomy to the testis and determined that the spermatic artery is an end artery. The parenchyma of the testis supplied by this artery would become ischemic if it were transected close to the testis. Ligation as far from the testis as possible is recommended to maximize collateral blood flow [87].
- Testicular autotransplantation may be performed by microvascular anastamosis of the testis to the ipsilateral inferior epigastric artery and vein.
- Rarely, a two-stage orchiopexy may be performed without division of the spermatic vessels when the Prentiss maneuver and cord dissection have failed to gain adequate length. The testis is anchored in its most dependent position (high scrotum or pubic tubercle) with or without the cord covered by a Silastic sheath. The second stage is employed 6 to 12 months later.

Controversy exists as to the method of testis fixation. The surgeon's choice has included a subcutaneous pouch with suture fixation versus a sutureless subdartos pouch. Bellinger et al [88] have shown that sutures through the tunica albuginea cause testicular parenchymal damage in the rat. Chromic sutures produce more fibrosis than permanent sutures. The least fibrosis occurs with a sutureless subdartos pouch. Jarow [89] determined that subtunical sutures might damage the testicular blood supply, more in the lower pole than in the upper pole.

Nonpalpable testis

Exploration for a nonpalpable testis may occur through an extended inguinal incision, an abdominal incision, or, more commonly, via diagnostic laparoscopy. At the time of exploration, three main findings are likely to be encountered: (1) blind-ending spermatic vessels above the internal inguinal ring (44%), (2) an intra-abdominal testis (36%), and (3) cord structures (vessels and vas) that enter the internal ring (20%). Blind-ending vessels diagnose the entity of vanishing testis syndrome, most likely owing to an early prenatal vascular event. A blind-ending vas deferens or spermatic vessels that are not seen warrant further exploration of the retroperitoneum up to the level of the renal hilum to document the presence or absence of testicular vasculature. Cord vessels entering the ring warrant an inguinal exploration for identification of a testis or a testicular nubbin. If a testicular nubbin is found within the scrotum, some surgeons recommend contralateral scrotal testis fixation owing to the possibility of a previously unrecognized torsion. Options for the treatment of an intra-abdominal testis are varied and depend on the patient's age, testis size, contralateral testis, and the skills of the surgeon (Table 1) [90].

Long-term prognosis

Patients with cryptorchidism have two major concerns: (1) an increased incidence of testicular cancer and (2) a heightened risk of subfertility [91–93].

Table 1
Surgical techniques for nonpalpable testes

Orchiopexy type	Description	Success rate
Standard abdominal orchiopexy	Extended inguinal vs abdominal incisions are performed (vertical midline or Pfannenstiel); may proceed to other techniques for orchiopexy (ie, two stage, artery ligation), depending on testis mobility.	81% (scrotal testis without atrophy) 82% success ("peeping" testis at internal inguinal ring) 74% (abdominal cavity)
Two-stage orchiopexy	Can be used after extensive cord mobilization, but there is a risk of spermatic cord injury at second procedure.	73%
Fowler-Stephens: one-stage	Must plan ahead to avoid devascularization of the secondary blood supply from the vas deferens and the cremaster muscles.	67% (open or laparoscopic)
Fowler-Stephens: two-stage	Theoretically allows improved collateral blood supply, but requires a second stage; open or laparoscopic.	77% (literature review reveals no statistically significant difference between success rates of one vs two-stage Fowler-Stephens orchiopexies)
Laparoscopy-assisted orchiopexy	Mobilization of the testicular vessels is performed laparoscopically up to the renal level to avoid tension for a classic open inguinal orchiopexy; increased magnification aids dissection; use abdominal port incisions and open inguinal incision.	100% (small study population)
Microvascular orchiopexy	Provides adequate scrotal position with preservation of spermatic artery blood flow; requires special expertise.	84%
Orchiectomy: open or laparoscopic	Usually performed laparoscopically.	100%

Testicular malignancy

Cryptorchidism has been positively related to testicular cancer. The incidence of malignancy in a cryptorchid testis is 1 in 500 for American males [94]. The combined risk for all cryptorchid boys is 20 to 46 times higher than for boys with normally descended testicles [95]. Cromie reported a four-fold increase in the risk for cancer in an abdominal cryptorchid testis in a comparison with inguinal undescended testes [93]. The increase in the incidence of malignancy in cryptorchid testes warrants close follow-up, especially after puberty. Every cryptorchid boy should be taught how to perform a testicular self-examination, and parents should be made aware of the fact that, although orchiopexy enables early detection, it does not necessarily decrease the risk for testicular cancer.

Fertility

Formerly bilaterally cryptorchid men have greatly reduced fertility when compared with unilateral cryptorchid men and the general male population. Lee et al [96] reported a paternity rate of 62% (38% infertile) for bilateral cryptorchid men compared with a rate of 94% for a matched control group (6% infertile), indicating a six times increased risk. In contrast, unilaterally cryptorchid men had a paternity rate of 89.5%. Although this represents a twofold increase in infertility, this rate is similar to the level of infertility found in other studies of the general population. Examination of subfertility, or the time to pregnancy, shows that bilaterally cryptorchid men have greatly increased waiting times to pregnancy (33.9 months compared with 11.1 months for unilaterals and con-

trols). Lee et al [97] also examined the association of pretreatment testis location with fertility rates and various hormone levels (inhibin B, LH, FSH, testosterone) in adulthood. They concluded that "preoperative testis location in men with previous unilateral cryptorchidism is not a major determinant of fertility according to paternity, sperm count, or hormone levels." Although semen quality may be impaired in men with a unilateral cryptorchid history, there has not been an excellent correlation among an impaired semen analysis, decreased fertility index (number of spermatogonia/50 tubules), and paternity. An Ad spermatogonia count or other unidentified molecular markers may be a more useful indicator of fertility (and paternity) in these patients.

Summary

Research efforts to define the pathophysiology of cryptorchidism and its sequelae have rapidly advanced in the past 10 years. Surgical techniques have been refined to the degree that 6- to 12-month-old cryptorchid boys are repaired with great success. The goals of future studies will be to identify those boys who are at increased risk for infertility or malignancy to intervene early and change their outcome.

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Voiding dysfunction in children

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The two most common presentations of voiding dysfunction in children, urinary incontinence and urinary tract infections (UTIs), constitute a significant proportion of visits to the practicing urologist. UTIs occur in 7.8% of girls and 1.6% of boys in Sweden by 7 years of age [1], and are associated with uncomfortable symptoms and expensive antibiotics. Vesicoureteral reflux is associated with bladder dysfunction (15%–50%) [2] and an increased treatment cost compared to patients with reflux who void normally [3]. Reflux may be resolved faster after management of voiding dysfunction [4].

Wetting causes considerable anxiety in children and parents. By 7 years of age, 6% of girls and 3.8% of boys continue to have problems with daytime wetting [5]. Children with a history of UTI have a higher prevalence of daytime wetting than those without [6]. Older children consider wetting in school the third-worst stress, following the death of a parent and going blind [7]. Women who recall a history of daytime urinary symptoms are more likely to have urge incontinence [8]. Despite the frequency and vexing nature of voiding dysfunction, physicians may not always obtain a careful history to identify and properly treat children with this condition. This article addresses the diagnostic and therapuetic approach to such children.

Definitions

The International Continence in Children Society has provided standard definitions of lower-tract dysfunction in children [9]. *Incontinence* implies urinary leakage, rather than soaking, and can occur during the day or night. *Enuresis* is complete expulsion of urinary contents after a period where urinary control is anticipated. Generally, children are expected to be dry during the day by 4 years of age and at night by 5 years of age. *Nocturnal enuresis* is wetting during the night and *diurnal enuresis* is wetting during the day. A condition is *primary* if there has been no dry period longer than 6 consecutive months and *secondary* if a dry period has lasted 6 months. *Monosymptomatic nocturnal enuresis* describes bedwetting exclusively, with no daytime concerns; in *polysymptomatic nocturnal enuresis*, complaints such as UTI, urinary urgency, frequency, or wetting may coexist. The latter condition is usually more difficult to treat.

Dysfunctional voiding as a broad term to describe functional incontinence or UTI is a misnomer because it describes inappropriate relaxation with micturition, a subset in a broader category of lower–urinary tract dysfunction. Some have labeled children with these symptoms as having *dysfunctional elimination syndrome* to include the important relationship between bowel and bladder [10,11], because although the systems are thought to be independent, conditions affecting one system significantly affect the other.

Developmental aspects of bladder control

Children usually follow a predictable course of continence for bowel and bladder, although the mechanisms to achieve continence are not understood completely. First, bowel control is established at night, followed by bowel control during the day. Soon after, bladder control is achieved during the day, usually between 24 months and 4 years of age. Finally, children remain dry at night.

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Voiding in infancy traditionally has been thought to be reflexive, with the brain having a passive role in coordinating the flow. The child less than 1 year of age voids about once an hour with contractions under the control of the pontine mesencephalic micturition center in the brainstem [12]. Recent studies have shown that the cortex is stimulated in infants and that infants awaken when they void at night. Furthermore, bladder instability is not the rule; infants do not always void in a coordinated fashion, which suggests they contract their pelvic floor musculature [13]. As children get older, bladder capacity increases and the ability to empty improves. By 3 years of age voiding is uninterrupted and voiding frequency decreases to approximately two times over a 4-hour observation period [14].

Three important accomplishments occur during toilet training. First, the toddler develops the ability to sense bladder fullness and inhibit bladder contractions. Second, the ability to void volitionally develops as the toddler relaxes the pelvic floor and the bladder contracts. Finally children are able to contract their sphincter during voiding, if they choose, and stop voiding.

The frequency of voiding decreases with age such that 6-year-old children void approximately five to six times per day, with most voiding between three to eight times per day [6]. This decrease occurs because bladder capacity increases with age, and because fluid intake is decreased as the child relies on table food for nutrition. Although a nonlinear model is most accurate for determining expected bladder capacity for age, two practical linear equations have been determined [15]:

$$(2 \times \text{years of age}) + 2 = \text{bladder capacity (ounces) for children less than 2 years of age}$$

$$\text{years of age}/2 + 6 = \text{bladder capacity (ounces) for children 2 or more years of age}$$

Some approximate the normal bladder capacity in ounces by adding 2 to the child's age in years.

Etiologies of incontinence and infections

Before assuming that a patient has a functional disorder, one must exclude organic pathology. Therefore, a comprehensive classification scheme to assist the clinician in directing the history, physical examination, and appropriate laboratory and radiographic studies is useful. Box 1 lists causes associated with wetting and infection [16].

Box 1. The ABCs of incontinence and infection

Anatomic
Congenital
- Ectopic ureters
- Epispadias
- Posterior urethral valves
- Urogenital sinus
- Vesicoureteral reflux
- Vaginal voiding

Acquired
- Labial adhesions
- Tumor
- Traumatic

Behavioral
- Attention deficit disorder (with or without hyperactivity)
- Sexual abuse
- Stress
- Toilet avoidance

Central nervous system/neurogenic
- Cerebral palsy
- Epilepsy
- Multiple sclerosis
- Myelodysplasia
- Syringomyelia
- Tethered cord
- Tumor

Developmental
- Giggle micturition
- Primary nocturnal enuresis
- Urge syndrome

Endocrine/renal
- Chronic kidney disease
- Diabetes insipidus
- Diabetes mellitus

Functional
- Dysfunctional voiding
- Encopresis/constipation
- Hinman syndrome

Genetic
- Ochoa syndrome
- Williams syndrome

Habit
- Infrequent voiding
- Poor toileting habits

Infective/irritative
Foreign body
Hypercalciuria
Interstitial cystitis
Pinworms
Urethritis
UTI (as a cause of incontinence)
Vulvovaginitis

Adapted from Abidari JM, Shortliffe LM. Urinary incontinence in girls. Urol Clin North Am 2002;29:661–75.

Because toilet training is a developmental milestone, it is not surprising that children with developmental delays will take longer to accomplish this task. Additionally, perturbations that arise during toileting may explain why some children develop functional voiding difficulties during the day. Irritative voiding symptoms caused by chemical irritation, recurrent UTIs, and constipation can cause children to contract their external sphincter inappropriately because they fear pain, as well as increase the bladder's likelihood to contract without central inhibition. McKenna and colleagues [17] postulate that neuroplasticity caused by the stimulation of trophic factors may cause changes in bowel and bladder innervation. These changes may decrease the functional bladder capacity and increase chances of wetting and, in some cases, UTI. Infections perpetuate this cycle by reinforcing the child's fear of urinating, just as constipation inhibits effective defecation.

Types of voiding dysfunction

The *urge syndrome* is characterized by frequent attacks of the need to void countered by hold maneuvers such as squatting [18]. The urine loss is usually mild, with dampening of the undergarments. A nocturnal component also may be present with dampness but not saturation. These children void frequently. Some children experience suprapubic or perineal pain during contractions [19]. The signs and symptoms are caused by uninhibited detrusor contractions countered by voluntary contraction of the pelvic floor to minimize wetting, creating enormous intravesical pressures. The functional capacity of the child's bladder is small for age.

Staccato voiding is characterized by periodic bursts of pelvic floor activity causing increased detrusor pressure coinciding with dips in the urine flow rate. The flow time is prolonged and emptying may not be complete, increasing the child's risk for developing UTIs. Staccato voiding may be seen in conjunction with urge syndrome.

Fractionated voiding is characterized by incomplete, infrequent voiding with micturition in small fractions. The bladder capacity is large for age and urge is inhibited easily. Abdominal pressure (Valsalva) is necessary to shorten the flow time. The flow rate is irregular because of the reflex activity of the pelvic-floor muscles. Wetting in these patients is usually secondary to overflow incontinence. UTIs are common because emptying is incomplete.

Lazy bladder syndrome is the result of longstanding fractionated voiding. These children void infrequently and strain to empty because detrusor contractions are virtually absent. Large postvoid residuals and UTIs are common.

Hinman syndrome, first described by Hinman [20] in 1973, may be the most severe form of voiding dysfunction. This condition is characterized by detrusor overactivity, followed by bladder-sphincter dyssynergy, followed by detrusor decompensation. Radiographs show thick trabeculated bladder walls, vesicoureteral reflux, and reflux nephropathy. Psychologic "failure personalities" were described as a possible etiology [20]. Surgical treatment before correcting this imbalance may lead to significant complications and is discouraged [21].

Diurnal enuresis is associated with normal but infrequent voiding. These children, usually boys, delay emptying until it is too late. Therapy aimed at increasing voiding frequency is usually successful. An association with behavioral problems in these children has been suggested [22].

Children with *benign urinary frequency (pollakiuria)* suddenly need to void frequently, as often as 30 times per day [23]. They do not complain of dysuria and rarely wet during the day. Once asleep, these children do not awaken and do not wet their bed. UTI should be excluded. This condition is self-limited, is believed to be related to stress, and responds to reassurance. A recent study suggests a relationship between this behavior and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections in some children [24].

Girls with *vaginal reflux* complain of leaking after standing or of incomplete emptying and the

need to void again. They often wipe themselves excessively, irritating the perineum. Vaginal reflux is likely to occur if girls void with their legs together. Advising these girls to void with their legs straddling the toilet may be helpful. Labial fusion should be excluded on examination.

Almost exclusively seen in girls, *giggle micturition* is associated with the complete expulsion of bladder contents on laughing. This embarrassing condition is often confused with stress incontinence, which is uncommon in children. In many cases, a detailed history will suggest these patients have symptoms such as urge, with improvement after the use of anticholinergic agents [25]. In its pure form, however, affected girls have no symptomatology between episodes. Giggle micturition may be related functionally to cataplexy and has responded to stimulants such as methylphenidate in uncontrolled studies [26].

Vesicoureteral reflux and voiding dysfunction

Increased intravesical pressure can promote reflux through a marginally competent vesicoureteral junction. Investigators have identified detrusor instability and a history of voiding dysfunction in a large proportion of children with reflux [27,28]. Reflux may be identified before the knowledge of voiding dysfunction as part of the evaluation for UTI. It is important, therefore, to obtain a history that includes questions focusing on voiding behavior. In many cases, reflux resolves after treatment of voiding dysfunction without the need for surgery [4,29,30], although breakthrough infections may develop that prompt the need for surgical correction [31]. Theoretically, surgical treatment alone does nothing to help children with their voiding problems. Although open surgery is effective in such children, treatment specifically aimed at reducing elevated detrusor pressures should be undertaken before and after surgery because postsurgical infections develop [32]. Early reports on endoscopic antireflux surgery with dextranomer/hyularonic acid copolymer on similar patients have not been as favorable [33].

Evaluation

A complete history and physical examination are essential to identify children with a neuropathic etiology for their incontinence, to identify obstructive lesions, and to distinguish between the different forms of functional incontinence. Daytime wetting or recurrent UTIs are the hallmark complaints associated with dysfunctional voiding. Wetting is usually prevalent in the afternoon because most children are anxious about wetting in school and work hard to stay dry.

A voiding diary is useful to determine a child's voiding frequency and volumes. Children with urge syndrome void at least seven times per day. Children with advanced stages of dysfunctional voiding may void infrequently and strain or use manual pressure to empty.

Sudden and imperative sensations of urge, several times a day, are characteristic of the urge syndrome. Despite the use of hold maneuvers such as Vincent's curtsy [34] to prevent leakage, these children will dampen their pants. Children with lazy bladder syndrome rarely demonstrate urge. Children with diurnal enuresis deny urge and ignore uncontrolled wetting.

One should inquire about a history of recurrent UTIs, which may be secondary to dysfunctional voiding with incomplete emptying as the inciting factor [35,36]. Incontinence in conjunction with stress may be seen in children with urge syndrome when increased abdominal pressure evokes a detrusor contraction. Constipation and fecal soiling are seen commonly in children with dysfunctional voiding because children with sphincter dyssynergy also may postpone defecation [37]. Conversely, constipation causes postvoid residuals and hydronephrosis, with significant improvement seen after treatment [38,39]. These studies underscore the importance of obtaining information regarding bowel function.

Unfortunately most parents do not know the bowel habits of their children. Specific questions must be asked about fecal staining; the frequency, caliber, and volume of bowel movements; the presence of abdominal pain; and the child's relationship to defecation.

A family history of day and night wetting should be obtained. A strong genetic predisposition has been identified in primary nocturnal enuresis and recent data show a correlation between children with moderate to severe daytime wetting and their parents [40].

A social history that includes how wetting affects the child is essential to assess motivation, a key element of success in any behaviorally oriented program. School performance, attention deficit disorder (with or without hyperactivity), and a history of problems with sensory

integration, such as avoiding loud noises and certain tactile stimuli, may play a role in voiding abnormalities [41].

The physical examination is usually unrevealing, but the back should be examined for sacral malformations, lipomas, hemangiomas, hairy patches, and asymmetry of the gluteal crease. The presence of spina bifida occulta alone, however, does not portend a poorer prognosis compared with similar children without spine anomalies [42]. Abnormal tone on rectal examination, absent perineal sensation, and an absent bulbocavernosis reflex can be confirmatory of a neurogenic etiology for wetting. Inspection of the genitalia for meatal stenosis in boys and labial fusion in girls should be performed. The neurologic examination should include careful attention to the lower extremities, including tone, strength, sensation, and reflexes.

In children with daytime symptoms, a urinalysis and urine culture should be obtained. A renal and bladder ultrasound performed before and after voiding can be useful to identify obstructive uropathy, ureteroceles, and functional bladder capacity. Children with recurrent afebrile UTIs or one episode of a febrile UTI, as well as boys with thick-walled bladder and poor stream, should have a voiding cystourethrogram to identify vesicoureteral reflux and posterior urethral valves. Some patients demonstrate a peculiar anomaly on the voiding cystourethrogram: the spinning-top configuration of the posterior urethra (Fig. 1). This anomaly seems to be secondary to the force of the detrusor on the closed external sphincter, causing dilatation of the posterior urethra [43]. A scout film of the abdomen can determine if there are bony abnormalities of the spine or severe constipation. In some cases an MRI of the lumbosacral spine is necessary to exclude spinal-cord anomalies.

Urodynamic testing is reserved for children who do not respond to conservative treatment. This study can be done in children of any age, although it is easier to interpret results when the patient is cooperative. Uroflowmetry determines the voiding profile, including the velocity and flowtime. A normal flow should be continuous and uninterrupted [44]. Coupled with ultrasonography to establish the presence or absence of a postvoid residual, this tool can assess pelvic floor relaxation indirectly. The composite data derived from the history, physical examination, radiographic studies, uroflow, and urodynamic study (if performed) assign patients into the broad classifications of voiding abnormalities.

Fig. 1. Spinning top urethra in a girl with left vesicoureteral reflux.

Therapy

After determining that there is no anatomic or neuropathic etiology for incontinence and infections, the author recommends a stepwise treatment regimen that increases in complexity pending each patient's response. This interdisciplinary approach uses various team members with individual strengths to assist the patient and his or her family. The author's approach includes:

Step I: Bowel program
Step II: Regular voiding while avoiding irritation
Step III: Relaxing the pelvic floor—biofeedback
Step IV: Increasing functional bladder capacity—anticholinergic medication
Step V: Difficult cases: psychology, clean intermittent catheterization, other therapies

Bowel program

For several years, investigators have reported that proper management of constipation or large, infrequently passed bowel movements with little attention to the bladder reduces wetting and UTIs [37,39]. In many cases it is difficult to convince parents that their child has large fecal boluses. Koff has suggested weighing children before and after the effective administration of laxatives. A weight loss greater than 0.9 kg suggests significant fecal retention.

The author advocates a series of enemas followed by the administration of laxatives, such as polyethylene glycol (Miralax) without electrolytes, or lactulose. Children are advised to sit in a comfortable position with their resting their legs on a stool twice a day after meals to take advantage of the gastrocolic reflex. High fiber intake and water also are encouraged strongly to maintain good bowel health. The American Academy of Pediatrics recommends that children and adolescents consume 0.5 g of dietary fiber per kg of body weight, up to a maximum of 35 g/d [45]. The American Health Foundation recently recommended that children and adolescents consume grams of dietary fiber equivalent to their age in years plus 5 g/d [46]. Physicians can review sources with recommendation to increase a child's fiber intake [10,47].

Patients are encouraged to keep elimination diaries and have bowel movements that are neither small, hard pellets, nor voluminous boluses. Over time, stool softeners can be removed while the child remains on high fiber intake indefinitely.

Eliminating inflammation

Generally, individuals feel relief after voiding. If a child experiences discomfort with voiding, however, it becomes an unpleasant task that is likely to be averted or performed improperly. Therefore, anything that causes irritation should be suppressed. The author recommends increasing water to dilute urine and eliminating caffeine, carbonation, citrus juices, and chocolate, which the author believes are bladder irritants. The perineum of young girls who wet is often inflamed. Emollient creams may be applied, if tolerated, whereas soap is avoided. Soaks in baking soda and water also may be beneficial.

Children with recurrent UTIs enter a cycle of pain, causing poor relaxation that increases the risk of subsequent infections. In some cases a short course of antibiotic prophylaxis (trimethoprim-sulfamethoxazole, 2 mg/kg, or nitrofurantoin, 1–1.5 mg/kg) is used to attempt to break the cycle [16].

A voiding schedule is used to teach children to have their "brain be the boss of their bladder." Diaries are used to help children void about every 2 hours, or six times per day. It is important to ask teachers to remind patients discreetly to void during breaks rather than allow them free access to the restroom. Watches that quietly beep or vibrate can be used to remind them to void.

Biofeedback

A program aimed at retraining the child to remain continent and empty effectively would be the best approach to manage these patients, assuming the child has sufficient cognitive ability to understand what they are being taught and provided that feedback can be incorporated into the training. Biofeedback is the use of modern instrumentation to give a person better immediate information about a specific physiologic process controlled by the central nervous system, but not perceived clearly or accurately [48]. Urodynamic signals such as urine flow rate, pelvic floor electromyogram, or detrusor pressure are suited perfectly for biofeedback [49–52].

Different methods of biofeedback have been used. Initially, the author used real-time uroflow to teach children directly how to relax the pelvic floor as they void. The author and others also have used Kegel (contraction/relaxation) exercises to teach children how to isolate and control their pelvic floor musculature [53,54]. McKenna and colleagues [17] have used interactive games in a series of biofeedback sessions to optimize success. Ultimately, the author found little difference in the methodology with regard to reducing incontinence and UTIs, but children must be encouraged to practice their exercises at home and listen to their flow to verify their ability to relax [55].

Anticholinergic treatment

Anticholinergic medications are helpful for children with urge syndrome and reduce the degree of vesicoureteral reflux by decreasing the number of uninhibited detrusor contractions and increasing functional capacity [56–58]. Short-acting

Table 1
Medications for incontinence

Medication	Dose	Adverse events	Comments
Oxybutynin HCl	2.5–5 mg bid to qid (0.2 mg/kg/dose)	Dry mouth, flushing, blurry vision, constipation, heat intolerance	Short-acting preparation Available as 5-mg tablet or 5mg/5ml syrup FDA-approved in children
Long-acting oxybutynin (Ditropan XL)	5–15 mg/d	Same as above	Must be taken without chewing FDA-approved in children Available as 5-, 10-, and 15-mg tablets
Tolterodine tartrate	1–2 mg bid	Same as above; may be less intense than oxybutynin	Use lower dose with *CYP3A4* inhibitors Available as 1- or 2-mg tablets
Long-acting tolterodine (Detrol LA)	2–4 mg/d	Same as above	Same as above May be sprinkled on food Available as 2- or 4-mg capsules
Long-acting hyoscyamine (Levbid)	0.375–0.75 mg bid	Same as above; more problems with visual accommodation	May not be chewed; may be halved Available as 0.375-mg tablets FDA-approved in children (short-acting)
Doxazosin	0.5–1 mg/d	Hypotension, dizziness	Alpha-blocker may help relax internal sphincter

preparations used in the past largely have been replaced by long-acting preparations (Table 1), although the US Food and Drug Administration (FDA) has approved only one of these medications for use in children. Recent uncontrolled studies have shown promising results in children using the long-acting forms of tolterodine and oxybutynin [59,60]. Regardless of the medication selected, emphasis should remain on proper bowel habits and frequent urination. The author assesses the child's flow and bladder emptying regularly while they are taking anticholinergic medication.

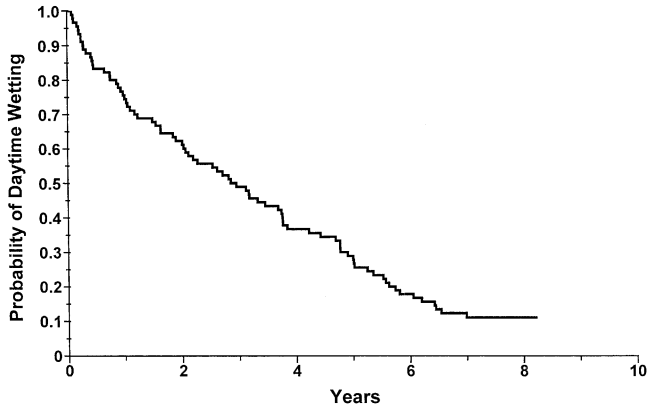

Fig. 2. Probability of remaining dry during the day after being seen in the author's program. (*From* Saedi N, Schulman SL. Natural history of voiding dysfunction. Pediatr Nephrol 2003;18:994–7, with permission.)

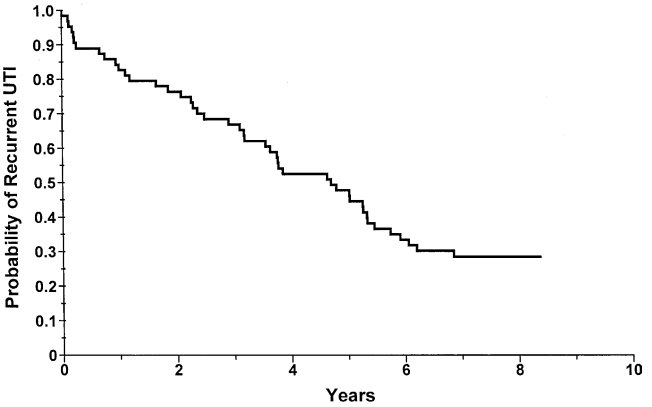

Fig. 3. Probability of recurrent urinary tract infections after being seen in the author's program. (*From* Saedi N, Schulman SL. Natural history of voiding dysfunction. Pediatr Nephrol 2003;18:994–7, with permission.)

The overall results using medication may be temporary, with more success seen when medications are used in conjunction with a well-organized treatment program.

Other treatments

When children do not respond to these measures, the clinician should reevaluate the etiology for the treatment failure. In many cases there may be problems with treatment adherence because of comorbid factors such as attention deficit/hyperactivity disorder, learning disabilities, or sensory integration issues, or because of problems in the family [41]. In such cases, psychologic counseling can be invaluable [61].

Clean intermittent catheterization (CIC) has been a useful tool in children with persistently elevated postvoid residuals, such as those with lazy bladder syndrome. Pohl and colleagues [62] instituted CIC in 23 such children. Sixteen children tolerated the treatment and improved clinically.

Alpha adrenergic blockade (doxazosin, 0.5–1 mg/d) is beneficial in some children with inadequate bladder emptying [63]. Neuromodulation has been reported to help children with recalcitrant urge syndrome [64,65]. Randomized, controlled studies are needed to verify these initial reports.

Prognosis

Only isolated reports have documented the long-term outcome of children with voiding dysfunction. Kuh and colleagues [8] reported that women who at 6 years of age had wet in the day or several nights per week were more likely to have severe incontinence and report urge symptoms. Curran and colleagues [66] reported that most children with idiopathic detrusor overactivity improved from a conservative method of treatment, including the use of anticholinergic treatment. With an average resolution time of 2.7 years, 87% had complete or significant symptom resolution. The author has shown that after over 6.5 years of follow-up in 99 children, 91% no longer wet during the day (Fig. 2), 84% no longer wet at night and, among those with a history of infection, 82% no longer have infections (Fig. 3) [67]. It remains difficult to assess the direct effect of the author's treatment versus the natural history of this condition.

Summary

Children presenting with daytime wetting and recurrent infections require thorough histories and physical examinations to exclude organic pathology. Careful attention to bowel habits is mandatory. The evaluation and treatment of these children should be stepwise and comprehensive. The prognosis of most of these children is favorable.

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Nocturnal enuresis: medical management

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Nocturnal enuresis is a common presenting complaint, with 5 to 7 million children affected in the United States. Although it is generally benign, nocturnal enuresis can cause significant frustration for parents and the affected child. More importantly, it can lead to diminished self-esteem of the affected child. This article briefly reviews current thoughts on the etiology of this disorder, discusses the evaluation of patients, and then focuses on available medical therapy. The reader is referred to the article on behavioral treatment elsewhere in this issue for a review of nonmedical treatment. Although they are separated in the organizational schema of this issue, these modalities can compliment each other.

Definitions

Nocturnal enuresis can be defined as the involuntary passage of urine during sleep beyond the age of anticipated nighttime bladder control, which is generally accepted as 5 years of age. It can be divided into primary and secondary forms. Primary nocturnal enuresis is defined as bed-wetting in patients who have never been dry for an extended period. Secondary nocturnal enuresis is the recurrence of nighttime wetting after 6 months or more of dryness. Nocturnal enuresis may also be classified as monosymptomatic and polysymptomatic. Monosymptomatic nocturnal enuresis is bed-wetting associated with normal daytime urination. Children with polysymptomatic nocturnal enuresis have bed-wetting associated with other bladder symptoms, such as urgency, frequency, or other signs of bladder instability. These distinctions are important when evaluating the patient, because they determine the appropriate work-up and therapy. Eighty percent to 85% of children with enuresis have monosymptomatic nocturnal enuresis [1].

Prevalence

Approximately 15% of children wet the bed at night when they are 5 years old. There is a spontaneous resolution rate of about 15% per year; therefore, by age 15 years, only about 1% of adolescents have a problem with nocturnal enuresis [2]. The relatively high incidence of enuresis in young children and the spontaneous cure rate should be conveyed to parents and the child as a means of reassurance.

Etiology

The etiology of nocturnal enuresis is not completely understood. The condition probably has a multifactorial etiology. Several theories have been proposed to explain enuresis, including genetic factors, abnormal urodynamics, alterations in vasopressin secretion, sleep factors, psychologic factors, organic disease, and maturational delay.

Genetic factors

There is strong evidence of a hereditary basis for nocturnal enuresis. Bakwin showed that when both parents had a history of enuresis, there was a 77% incidence in their children [3]. If one parent had a history of enuresis, the incidence decreased to 44% in children. If neither parent had a history

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of enuresis, only 15% of their children had enuresis. Furthermore, the parental age of resolution may be predictive of when the child's enuresis will resolve [4]. Twin studies also support a genetic basis for enuresis. The concordance rate is much higher in monozygotic twins (68%) when compared with dizygotic twins (36%) [5].

Several chromosomes have been found to have a genetic linkage to nocturnal enuresis. Using linkage analysis, Danish researchers were the first to report an unidentified enuresis gene (ENUR1) in chromosome region 13q [6]. Later studies have also shown linkage to chromosome 12q and chromosome 22 [7,8]. Despite these known linkages, a specific gene has yet to be identified.

Diminished bladder capacity and abnormal urodynamics

As children grow, their bladder capacity increases. Newborns have a bladder capacity of about 1 to 2 oz (1 oz = 30 mL) [9]. Adult bladder capacity is approximately 12 to 16 oz [10]. The bladder capacity in children can be estimated using the following formula: age (in years) + 2 = bladder capacity (in ounces) [11]. A reduced bladder capacity has been suggested to have an etiologic role in enuresis [12–15]. Troup and Hodgson [16] measured the bladder capacity of enuretic persons versus controls under general anesthesia. The enuretic children did not have reduced true bladder capacity despite their decreased functional bladder capacity. Other studies have shown that, when monosymptomatic nocturnal enuresis is isolated from other forms of enuresis, there is a low incidence of decreased bladder size [17].

The role of bladder instability as an etiologic factor in nocturnal enuresis has also been investigated. Urodynamic studies by Norgaard et al [18] showed that children with monosymptomatic nocturnal enuresis had bladder instability in 16% of daytime cystometrograms, which is a rate similar to that in normal controls. When nocturnal urodynamics were performed, the incidence of bladder instability increased to approximately 50%; however, nocturnal bladder instability was equally likely to lead to enuresis as it was to an arousal to void. In contrast to patients with monosymptomatic nocturnal enuresis, patients with polysymptomatic nocturnal enuresis have been shown to have a higher rate of functional bladder abnormalities [19].

Alterations in vasopressin secretion

In 1975, it was shown that vasopressin is released in a circadian rhythm, with increased secretion overnight [20]. This increased production is responsible for decreased urine production during the night. Ten years later, a Danish group showed that children with nocturnal enuresis did not have a normal increase in the nocturnal secretion of vasopressin [21]; however, the theory that nocturnal enuresis is the result of relative vasopressin deficiency is controversial. Other researchers have not found significant differences in nocturnal vasopressin secretion or nocturnal urine output between enuretic and nonenuretic children. Steffens et al [22] studied 55 children with nocturnal enuresis and found that only 25% of them had a significant decrease in nocturnal vasopressin levels in comparison with control subjects.

More recent studies have shown that the secretion of vasopressin may be influenced by bladder distention. When urine was diverted from the bladder, the normal circadian rise in nocturnal vasopressin secretion disappeared [23]. Furthermore, when the bladder was full during cystometry, vasopressin levels were higher than when it was empty. This finding suggests that an enuretic event may remove the stimulus for vasopressin secretion by emptying the bladder, perhaps explaining the low levels of vasopressin found in enuretics in prior studies. This theory is further supported by the work of Ohne [24] who showed increased activity in the hypothalamic cells that produce vasopressin within 2 hours of urethral obstruction in animal models.

Sleep factors

Many parents report that children with enuresis sleep more deeply and are more difficult to arouse than other children. This observation has led to the controversial hypothesis that children with enuresis have a sleep arousal disorder. Although some early sleep studies supported the theory, others report that the observation that children with enuresis are deep sleepers is biased by the fact that parents usually do not try to wake up children who do not wet the bed [9,25]. Controlled sleep studies have not found enuretic children to be sounder sleepers than their nonenuretic counterparts [26–28]. Nevertheless, a recent study did report that children with enuresis were more difficult to awaken in comparison with controls when exposed to the same auditory stimulus [29].

Early sleep studies also reported that bedwetting occurred when the child was in a stage of deep sleep [30]. Subsequent studies dispelled this theory, showing that enuresis occurred randomly through the night at different stages of sleep and in proportion to the amount of time spent in each stage [31].

An association between nocturnal enuresis and obstructive sleep apnea has been described [32,33]. Apneic episodes result in increased secretion of atrial natriuretic factor. This release results in inhibition of renin secretion, which leads to decreased aldosterone and increased diuresis. Tonsillectomy, adenoidectomy, or both have been reported to decrease nocturnal enuresis in as many as 76% of cases [33].

Psychologic factors

Psychologic factors in the etiology of nocturnal enuresis have been the focus of many investigations. Several studies have shown that children with enuresis do not have any difference in the incidence of psychologic disorders when compared with nonenuretic children [34,35]. Furthermore, Young and Morgan [36] found that treatment, such as an alarm device, was equally effective in disturbed and nondisturbed children. Secondary enuresis has commonly been attributed to psychologic stress, such as the birth of a sibling or divorce. Fergusson et al [37] found that children who had four or more stressful events in a year had an increased risk for secondary enuresis. Other investigators have not found such differences [38].

Some investigators have also postulated a relationship between attention-deficit hyperactivity disorder (ADHD) and nocturnal enuresis. Robson et al [39] suggested that children with ADHD were 2.7 times more likely than were normal children to have enuresis. The possibility that these disorders may be co-inherited was investigated by Bailey and colleagues [40] using a family study design. These investigators concluded that the pattern of inheritance they observed supported independent transmission of primary nocturnal enuresis and ADHD. Patients with both disorders may be ideal candidates for pharmacotherapy with tricyclic antidepressants.

Some researchers suggest that enuresis may lead to emotional disturbance. Stromgren and Thomsen [38] found that patients with primary nocturnal enuresis, in fact, had lowered self-esteem. Other studies have shown that children who undergo treatment for enuresis become happier and have an improved self-image [41,42].

Organic disease

When evaluating a child who presents with nocturnal enuresis, organic disease must be ruled out. Monosymptomatic nocturnal enuresis has a true organic cause in approximately 1% of cases [2]. Urinary tract infection is one possibility that should be considered; however, treating the infection rarely cures the enuresis [2]. This observation may indicate that the urinary tract infection could be the result rather than the cause of enuresis. Bacteriuria may have more of a causative role in children with secondary enuresis [43]. Spinal cord pathology, posterior urethral valves, an ectopic ureter, constipation, diabetes insipidus and diabetes mellitus, among others are conditions that need to be considered in the child with enuresis.

Maturational delay

A final hypothesis for nocturnal enuresis, which may be the most unifying of the etiologies presented, is that children with enuresis have a maturational delay in nervous system development. In a large population study, Jarvelin [44] found that children with enuresis had more fine and gross motor clumsiness, perceptual dysfunction, and speech defects than did controls. Furthermore, the study found that children with nocturnal enuresis were significantly shorter than controls. Patients with polysymptomatic nocturnal enuresis differed more from controls than did those with monosymptomatic nocturnal enuresis. Earlier studies also support the theory of developmental delay [45,46]. These studies suggest that achieving continence at night is a normal part of development, and that children with enuresis have a delay in acquiring this skill. Some children have other lags in development, but in most cases, these delays all improve with time.

Evaluation

Most children who present with enuresis do not require an extensive work-up. A thorough history and physical examination generally are sufficient to identify those who need further investigation.

History

When taking the history, the pattern of enuresis must be defined. One should determine the

number of nights per week the child wets and whether there are daytime symptoms. A thorough voiding history and detailed log should be obtained. The evaluation should include questions about polyuria, polydypsia, urgency, dysuria, an abnormal urinary stream, constant wetness, and a previous history of urinary tract infection. The pattern of nighttime fluid intake should be documented, as well as the intake of caffeinated beverages. Furthermore, one should ask about symptoms of constipation or encopresis, because approximately 15% of children with enuresis also have encopresis [9]. Other details in the history that should be elicited include problems during sleep (snoring, parasomnias), neurologic problems (changes in gait), and a developmental history. The examiner should always ask about a family history of enuresis, because this information is not always volunteered. The enuresis can usually be classified as primary or secondary.

Physical examination

Most children with a history consistent with primary nocturnal enuresis will have a normal physical examination. This fact not withstanding, a complete examination should be performed to evaluate for organic disease. Attention should be focused on the gastrointestinal, urogenital, and neurologic systems. When examining the abdomen, one should focus on whether there are any masses, such as a distended bladder or fecal impaction. The urologic examination should include an evaluation of the phallus and urethral meatus in boys and the introitus in girls. During the neurologic examination, one should evaluate the muscle tone, strength, sensation, and deep tendon reflexes of the lower extremities. The patient should be observed to determine whether he or she has an abnormal gait. The skin over the spine should be inspected for tufts of hair, sacral dimples, or vascular birthmarks that would suggest occult spinal dysraphism.

Laboratory and radiologic studies

All children with enuresis should have a screening urinalysis. The specific gravity should be checked to evaluate for diabetes insipidus. Glucose spillage suggests that diabetes mellitus is a concern. If the urinalysis or history is suggestive of urinary tract infection, a urine culture should be sent. It is the authors' practice to obtain a culture in all patients. Patients with monosymptomatic nocturnal enuresis do not need any further studies. Ultrasound of the kidneys and bladder with prevoid and postvoid residuals, a voiding cystourethrogram, and urodynamics should be considered in patients with polysymptomatic nocturnal enuresis or those with a concerning history or examination. Occasionally, the parents, the patient, or both will express significant concern that an anatomic abnormality is present. This concern is particularly common in older enuretic patients who have failed initial therapy. In these cases, it may be beneficial to perform a screening ultrasound to reassure the family that no anatomic problem is present. Once this test is performed, the patient and the parents can refocus on therapeutic options. Remarkably, this reassurance is sometimes all that the family is seeking from their visit to the "specialist."

Medical therapy

Treatment of nocturnal enuresis before the age of 6 years is rarely indicated. Parents who present with younger children should be reassured and counseled on age-appropriate norms. Treatment can generally be divided into behavioral therapy and medical management with pharmacotherapy. The reader is referred to the article by Dr. Blum elsewhere in this issue for a discussion of behavioral therapy.

Desmopressin

Desmopressin (DDAVP) is a synthetic analogue of vasopressin. DDAVP acts to decrease urine output by retaining water and concentrating urine in the distal tubules. The first controlled studies of DDAVP in enuretic children were published in the late 1970s [47]. DDAVP was approved by the US Food and Drug Administration in 1990 for the treatment of nocturnal enuresis. Moffatt et al [48] reviewed 18 randomized controlled studies of DDAVP in the treatment of nocturnal enuresis. All of the studies found a decrease in the frequency of wetting ranging from 10% to 91%, but only about 25% of the patients were completely dry while on the medication. Furthermore, in three studies including 123 patients, 94.3% of the patients relapsed after DDAVP was discontinued. The results of these studies indicate that, although DDAVP is significantly more effective than placebo for controlling enuresis, its primary utility is symptomatic control and not cure [49]. Husmann et al found that patients with monosymptomatic nocturnal

enuresis had a better response to DDAVP [19]. Sixty-eight percent of patients with monosymptomatic nocturnal enuresis had continence while on therapy versus 19% of patients with polysymptomatic nocturnal enuresis.

Predictors of response to DDAVP include nocturnal polyuria, fewer than three wet nights per week, only one enuretic event per evening, and a normal daytime bladder capacity based on age-specific norms [50]. DDAVP is available in an oral and intranasal form. The oral preparation comes as 0.2 mg tablets. The starting dose can be titrated up by 0.2 mg to a maximum of 0.6 mg. The initial dose of the nasal spray is 20 μg (one spray in each nostril) and can be titrated up to 40 μg. Alternatively, others recommend starting at the higher doses (0.6 mg or 40 μg) [51]. The drug should be administered 1 hour before bedtime, and patients should be treated for 3 to 6 months. A gradual taper of the medication should be performed, because abrupt discontinuation of therapy has been associated with higher relapse rates [1].

Studies have shown a similar efficacy with intranasal and oral desmopressin [52,53]; however, the authors recommend use of the oral form. Intranasal absorption is decreased when the patient has a cold or allergic rhinitis [54]. If patients are unable to swallow pills, the tablets can be crushed and given with food [55].

Side effects are infrequent but include nasal irritation, abdominal discomfort, nausea, and headache. A more serious side effect that has been reported in the literature is hyponatremic seizures [56–60]. Many of these cases have occurred in patients using DDAVP incorrectly. There have been no reports of hyponatremic seizures in controlled clinical trials. Because of the potential risk of hyponatremic seizures, it is reasonable to recommend nighttime fluid restriction.

Imipramine

Imipramine is a tricyclic antidepressant that has been used to treat enuresis since 1960, when its effect on enuresis was first described by an Australian psychiatrist [61]. The exact mechanism of its action is not known. It is believed to increase bladder capacity through a weak anticholinergic effect. An antispasmodic effect also exists, which decreases detrusor muscle contractions [10]. More recently, it has been suggested that imipramine may increase levels of antidiuretic hormone [62].

As many as 80% of children have significant improvement in enuretic events while taking imipramine [51]. There is wide variation in the reported cure rate. An analysis of data combined from eight double-blind controlled studies showed a long-term cure rate of 25% [63]. As is true for DDAVP, there is a high relapse rate when imipramine is discontinued, especially when treatment is ended abruptly, and the primary role seems to be symptomatic control.

The recommended starting dose of imipramine is 25 mg for children aged 5 to 8 years and 50 mg for older children and adolescents. If using a weight basis, the dosing is 0.9 to 1.5 mg/kg/day. Imipramine should be taken about 1 hour before bedtime. The duration of action is 8 to12 hours. Effects are generally seen within the first week of therapy, but it is recommended that therapy be continued for at least 2 weeks before assessing the efficacy and adjusting doses. Therapy should be continued for approximately 3 to 6 months, after which the dose should be weaned over 3 to 4 weeks.

Side effects from treatment with imipramine are uncommon but include personality changes, anxiety or nervousness, sleep disturbances, dry mouth, and gastrointestinal disturbances. Recently, a report of DNA damage in children taking imipramine for enuresis has appeared in the literature [64]. That report represents a limited study that remains unconfirmed by other investigations. Toxic overdose is a potential risk associated with imipramine. Its use has decreased greatly because of the low toxic/therapeutic ratio. Overdose can result in seizure, hypotension, coma, and fatal arrhythmias. When imipramine is prescribed, parents should be warned of the potential toxicity with overdose, especially if there are younger children in the house.

There has been interest in the use of other antidepressants, such as selective serotonin reuptake inhibitors, for the treatment of enuresis. An example of this class of drug would be fluvoxamine. Preliminary studies suggest that this class of medication is ineffective in the treatment of enuresis [65].

Oxybutynin

Oxybutynin is an anticholinergic and antispasmodic agent that decreases uninhibited bladder contractions. Its use in nocturnal enuresis has been extensively studied. As monotherapy in patients with monosymptomatic nocturnal enuresis, oxybutynin was shown to be no more effective than placebo [66]; however, oxybutynin is more

effective for patients with polysymptomatic enuresis and those with abnormal urodynamics [67]. The initial recommended dose is 5 mg at bedtime, which can be increased to 10 mg in older children. Side effects are common and include dry mouth, blurred vision, constipation, tremor, and flushing. Hyoscyamine is another anticholinergic agent that has been used in the treatment of enuresis.

Tahmaz et al [68] reported that combination therapy with oxybutynin and imipramine was more effective clinically than monotherapy. Another study also found that combination therapy for monosymptomatic nocturnal enuresis with an anticholinergic agent and an antidepressant was more efficacious than using either drug alone [69].

Other medications

Prostaglandin inhibitors such as indomethacin have also been studied in the treatment of nocturnal enuresis. Prostaglandins increase the tone of the detrusor muscle. Prostaglandin inhibitors may decrease resting bladder tone and increase continence by allowing an increase in bladder capacity. Prostaglandins also inhibit chloride reabsorption and the action of antidiuretic hormone. Prostaglandin inhibitors would decrease diuresis [19]. al-Waili [70] found that prostaglandin inhibitors decreased the number of wet nights from 19.5 to 3.6 per month. Another study found that patients with primary nocturnal enuresis had increased urinary nitrite excretion. Treatment with indomethacin significantly decreased urinary nitrite excretion and enuretic events; therefore, it has been suggested that nitric oxide and prostaglandins may have a role in the etiology of primary enuresis [71].

Stimulants have historically been recommended for use in enuretic patients. Indeed, these agents have been touted as an efficacious form of therapy as recently as the mid-1990s [72]. Although it is not uncommon to find individual practitioners who report anecdotal success with these agents, most of these drugs have been found to be ineffective, and their use is rarely recommended [73].

Summary

Primary nocturnal enuresis is a common problem, the etiology of which appears to be multifactorial. Currently, the mainstays of medical therapy are DDAVP, imipramine, and oxybutynin. The authors' first-line medication is DDAVP based on its reasonable efficacy and low potential for serious adverse effects. Imipramine is not used as a first-line drug owing to its potentially serious side effect profile. Use of this medication is reserved for selected patients who fail other forms of drug therapy, in particular those who are older and who have significant issues with self-esteem because of their enuresis. In these cases, the authors use imipramine in conjunction with psychology consultation. Oxybutynin is reserved for patients who fail monotherapy. As has been reported previously, some patients benefit from combination therapy [69,74]. One must recognize the important role of combining pharmacotherapy with behavioral modifications and behavioral therapy in patients with enuresis. Use of these combined modalities is commonly employed in the authors' practice.

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Nocturnal enuresis: behavioral treatments

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Nocturnal enuresis is increasingly understood as a biobehavioral problem. Medical and physiologic factors as well as behavioral and environmental factors have been implicated in the etiology. Pharmacologic and behavioral interventions are useful for treatment. Nevertheless, the ability to assess and understand how medical and environmental factors interact to cause some children and occasionally adults to wet the bed is still incomplete. Furthermore, although the study of enuresis has been increasingly rigorous over the last 30 years, the confidence in current explanations must be tempered somewhat by past missteps in the understanding and treatment of nocturnal enuresis.

Although explanations and treatments for nocturnal enuresis can be found dating from 1550 BC, the frequency at which the treatments were not only ineffective but in some cases harmful must be sobering to physicians treating this disorder today [1]. Indeed, even in the last 100 years, psychodynamic theories have attributed nocturnal enuresis to personality disorders or neuroses, leading to ineffective psychotherapy [2]. Moreover, medical treatments such as tricyclic antidepressants have been associated with rare cases of sudden death owing to accidental ingestion or overdose related to the belief that more medicine would result in greater benefit, and the use of desmopressin has been associated with hyponatremic seizures [3,4].

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The current understanding of the physiologic problems that contribute to nocturnal enuresis has focused on genetic factors, increased nighttime urine production caused by endocrinologic or other problems, difficulties with arousability from sleep, and an unstable bladder or low functional bladder capacity. These issues are discussed in detail elsewhere in this issue and are discussed herein to the extent that they have influenced the development or possibly explained the efficacy of behavioral treatments.

Given that there are no significant medical sequelae of monosymptomatic nocturnal enuresis, other than the possibility of a rash, the rationale for treatment is usually based on improving the child's or family's emotional or behavioral functioning. This article discusses the following questions related to the relationship between nocturnal enuresis and psychologic factors: (1) What is the evidence that psychologic factors contribute to the etiology of nocturnal enuresis? (2) What is the evidence that nocturnal enuresis leads to problems in behavioral and emotional functioning that can be remedied with treatment? The most commonly used behavioral treatments for nocturnal enuresis are described, and, when there is evidence, the factors influencing the efficacy of the treatment are discussed. The possibility of combining behavioral treatments with pharmacologic treatments is also discussed.

Definitions and epidemiology

Nocturnal enuresis is defined as bed-wetting after the age at which nocturnal bladder control is expected. This age is not universally agreed upon but is defined as age 5 years by the American Psychiatric Association [5]. Fifteen percent to 20% of 5 year olds, 7% to10% of 7 year olds,

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about 5% of 10 year olds, and approximately 1% to 2% of adults continue to wet the bed [6,7]. Any treatments for enuresis need to be compared with the spontaneous cure rate that is estimated to be approximately 15% per year [8,9].

Enuresis is defined as primary if the child has never had a 6-month period of time in which he or she was dry at night or secondary if the child begins wetting after a 6-month period of dryness. Children with nighttime wetting alone are often described as having monosymptomatic nocturnal enuresis to distinguish them from children with nocturnal enuresis in combination with daytime wetting or daytime urgency and frequency.

Effect of psychologic factors in the etiology of nocturnal enuresis

Nocturnal enuresis has been associated with increased rates of behavior problems and increased psychosocial adversity (eg, low socioeconomic status, divorce) [10–12]; however, the studies that have found these associations have tended to link all children with nocturnal enuresis together. In general, there is a much stronger association between secondary nocturnal enuresis and psychosocial adversity than for primary enuresis. For example, a longitudinal study of children from birth through age 15 years found no relation between adverse life events and primary enuresis, whereas a higher frequency of family conflict, financial difficulties, health, or bereavement issues were found to affect individuals with secondary enuresis [8,13]. The life event that seems to impart the greatest risk for nocturnal enuresis is divorce or prolonged separation from a parent for some other reason [11,14,15]. These events occur with increased frequency in the year before the onset of secondary nocturnal enuresis, suggesting that they may contribute to the etiology of this disorder [14].

In population-based studies, nocturnal enuresis is consistently associated with increased rates of behavior and emotional problems [12,16]. There does not seem to be a specific behavioral profile that characterizes children with nocturnal enuresis; it has been associated with an increased activity level, conduct problems, increased levels of anxiety, a depressed mood, decreased school achievement, problems falling asleep, and encopresis [15, 17–19]. Despite these associations, most children with nocturnal enuresis, particularly those with monosymptomatic nocturnal enuresis, do not have clinically significant behavior problems [15,20,21]. Furthermore, the nature of these associations is not well understood. Some studies suggest that behavior problems often precede secondary enuresis and may be related to the etiology of this problem [20], whereas others suggest that enuresis leads to psychologic or behavioral problems. It is also possible that enuresis and other behavior problems are influenced by a common risk factor. For example, a recent study that reported higher rates of behavior and emotional problems in children with nocturnal enuresis found that many, but not all, of the differences were no longer significant when one controlled for the fact that behavior problems and enuresis are associated with a low socioeconomic status [22].

Effect of nocturnal enuresis on psychologic problems

If a child has been evaluated and found not to have a medical disorder causing the nocturnal enuresis, in most cases, the enuresis will be self-limited, and the rationale for treating nocturnal enuresis must relate to the effect on psychosocial factors. Ample evidence suggests that nocturnal enuresis is stressful for families and children. For many children, it limits some social activities and causes feelings of guilt or shame [23]. Children with bed-wetting rate it as more stressful than being teased frequently or doing poorly in school [24]. Not surprisingly, it has been hypothesized that children with nocturnal enuresis have a lowered self-esteem or self-concept. Although three recent reviews found no evidence that most children with nocturnal enuresis have a significantly decreased self-concept [23,25,26], some children may be particularly vulnerable. For example, Theunis and colleagues [27] found that enuresis had more negative effects on self-concept in older children ($\geq$10 years) and in girls. Moreover, there is some evidence that treatment for nocturnal enuresis is associated with improvements in self-concept and a decrease in parent-perceived behavior problems [28–30]. How treatment results in these benefits is less clear. Some studies reporting a benefit in self-concept from treatment have found these effects regardless of the outcome of treatment, suggesting that the attention, support, and reassurance may have benefited all of the children in the studies [29,31]. In contrast, decreases in parent-reported behavior problems are more likely when the treatment is successful [29,30]. Repeated treatment failures may be associated with a lower self-concept [27].

Although nocturnal enuresis is clearly stressful for children and families and often leads to restriction in certain social interactions, for most children, it does not cause clinically significant decreases in self-concept. Nonetheless, support and reassurance are likely to improve the child's feelings about him or herself, even though these aspects of treatment may not directly decrease the symptom of night wetting. A treatment that decreases night wetting is likely to result in the greatest improvement in parent-reported behavior problems, but repeated unsuccessful treatments may contribute to decreases in self-esteem. Physicians treating this condition should be aware of the efficacy of all the available treatments and the factors that influence the chances of success.

Simple behavioral treatments

Fluid restriction

Fluid restriction is a logical intervention for nocturnal enuresis that is commonly recommended by physicians [32], but it has not been demonstrated to be effective. Most systematic behavioral interventions do not require fluid restriction, and some actually encourage increased fluid intake during at least some parts of the treatment (discussed in the section on overlearning and dry-bed training). Avoiding caffinated beverages that have a diuretic effect is a reasonable recommendation, although it has not been studied [7]. In the author's experience, this recommendation has often not been made before the time of referral for treatment.

Lifting and night awakening

Lifting refers to the procedure of taking the child to the toilet during the night to urinate without fully awakening him or her, whereas night awakening involves fully awakening the child to void shortly before he or she would usually wet the bed. Once the child is consistently dry on the awakening schedule, the frequency of the awakenings is decreased, or (for single awakenings) the time of the awakening is gradually moved to earlier in the night (eg, closer to bedtime) until the child is dry when awoken 1 hour after going to bed.

Parents commonly use lifting, but evaluation of the efficacy of this intervention has been limited. In a small study comparing lifting with a night-awakening procedure, both methods decreased the frequency of wetting, but the night-awakening procedure was more effective [33]. Lifting may also be discouraged, because it may teach the child to empty his or her bladder while asleep and deny the child the chance of associating a full bladder with waking [34]. Systematic night-awakening procedures are likely to be more effective than doing nothing but are not as effective as an enuresis alarm [35–37].

Retention control training

Retention control training is a behavioral intervention designed to increase functional bladder capacity in children with nocturnal enuresis. Children are given a fluid load and asked to hold voiding for progressively longer periods of time. The volume voided is recorded, and a small reward may be offered for increases in the volume [38]. Many small studies of retention control training have produced contradictory results [38,39,40]. It is clearly less effective than the enuresis alarm [41]. A recent relatively large randomized study compared 12 weeks of treatment with retention control training with treatment with desmopressin. At baseline, children were wetting at least 4 nights per week, and a positive response was recorded if the wetting frequency decreased to once every 2 weeks or less. Fourteen of 60 patients (23.3%) treated with retention control training had a positive response compared with 21 of 54 patients (38.9%) treated with desmopression [42]. On average, the children who had a positive response to retention control training had more than a twofold increase over their baseline functional bladder capacity, whereas the nonresponders to retention control training and the responders and nonresponders to desmopressin did not have a significant change in functional bladder capacity. In a subset of individuals with nocturnal enuresis and small functional bladder capacity, retention control training may increase functional bladder capacity, resulting in a decrease in the frequency of wet nights and, more rarely, the cessation of bed-wetting.

Enuresis alarm

The enuresis alarm is the most widely studied behavioral intervention for nocturnal enuresis. It consists of an alarm device and a moisture sensor that is placed under the sheets or, more commonly, attaches to the child's pajamas or underwear near the urethra. Urination during sleep triggers the alarm, which is designed to awaken the child. The mechanism by which the repeated pairing of urination during sleep with the alarm treats bed-wetting is not well understood. Initially, it was

thought that the alarm conditioned individuals to awaken when the bladder was full. Although this effect may explain the response in a subset of children, it does not account for the fact that more than 65% of individuals successfully treated with the alarm learn, on most nights, to sleep through the night without wetting [43,44]. Theories to explain this finding relate to conditioning of the pelvic floor muscle response or inhibition of detrusor contraction, which would be consistent with the finding that treatment with the enuresis alarm often results in an increase in nocturnal functional bladder capacity [45,46].

Two recent evidence-based reviews found ample data to conclude that the enuresis alarm is an effective treatment for nocturnal enuresis [47,48]. Alarms have been found to be more effective than medication in the long-term management of nocturnal enuresis [47,49]. Initial response rates (usually defined as 14 to 21 consecutive dry nights) vary considerably among studies, with most studies reporting response rates from 60% to over 80% [48]; however, there is a significant relapse rate that varies with how relapse is defined. If any wet night is considered a relapse, the rate is over 75% [50], suggesting that most successfully treated children will still have at least an occasional wet night. Most definitions of relapse require the child to wet the bed once a week or more for at least 2 to 4 consecutive weeks. Using this type of definition, relapse rates range from 30% to over 40% [50–53]. Although most relapses occur in the first 6 months after treatment [50,52], relapses more than a year after successful treatment are not uncommon. Even when relapses occur, most children are significantly improved over the baseline frequency of wetting [54]. Furthermore, even when this relapse rate is considered, the alarm has the best long-term efficacy of any behavioral or pharmacologic treatment for nocturnal enuresis. Of the families attending a urology referral center who elected to use the alarm, 56% reported that their child was dry 1 year later, whereas only 18% of those who elected treatment with desmopressin reported that their child was dry [55].

Despite the well-documented efficacy, treatment using the enuresis alarm is not without problems. A significant portion of children with nocturnal enuresis do not become dry at night when treated with the alarm, and the intervention is stressful for families. Dropout rates from treatment with the alarm are generally higher than with pharmacologic treatments. Some families do not tolerate the unscheduled and frequent night wakings. For nearly 75% of children, the alarm goes off more than once a night on at least some nights [50]. Initially, the alarm may not wake many children, and it may scare other children. Younger children usually require their parent's assistance during the night, resulting in sleep deprivation for the parent and child. When the child with enuresis shares a room with a sibling, the auditory alarm may also wake the sibling. The vibratory alarm may be an option in this situation, but if it does not awaken the child, it will not alert anyone else that the child has wet the bed, and studies have not been performed to document the efficacy of vibratory alarms. Added to these difficulties is the fact that treatment with the alarm tends to result in slow improvement, requiring 4 to 12 weeks or more.

Factors affecting the response to the alarm

The difficulties associated with use of the alarm have led to investigations of pretreatment and within-treatment factors that may help clinicians predict which children are likely to benefit from initial or continued use of the alarm. Parental intolerance of enuresis and higher levels of child behavior problems have been associated with premature termination of alarm treatment and lower rates of efficacy [50,56,57]. Unfortunately, although these families may be the ones most likely to be sent to urology referral centers, there are no studies that identify strategies that improve treatment success with these families. Other factors that have been associated with increased rates of treatment failure with the alarm include children who lack concern or motivation to change the problem, children with daytime wetting or low functional bladder capacity, developmental delays, and a variety of psychosocial stressors [43,50,51,56,58,59]. Most studies suggest that more severe pretreatment levels of wetting are associated with higher failure rates [43,56], whereas others have found no difference in failure rates or a better response to the alarm with higher pretreatment frequencies of wetting [52,59].

Within-treatment factors that influence outcome have been less well investigated. The percentage of nights that the child fails to wake in response to the alarm has been most consistently associated with decreased efficacy [43,60]. Inconsistent use of the alarm and triggering of the alarm early in the night have been associated with treatment failure in some studies but not others [43,61]. It is possible that the finding that triggering of the alarm early in the night is associated

with decreased efficacy is related to the fact that children are harder to awaken early in the night [61]. Ensuring that children are fully awakened and not just "lifted" to use the toilet and change the sheets when the alarm goes off seems to be critical to successful use of the alarm.

Combining the alarm with other behavioral treatments

The alarm has been used in conjunction with behavioral interventions that target some of the factors associated with treatment failure or the high relapse rate. The most frequently studied interventions include the use of retention control training to improve functional bladder capacity and overlearning to decrease relapse rates. Generally, adding retention control training to the enuresis alarm has not been shown to improve the overall efficacy of the intervention, although there is a suggestion in some studies that children may improve a little faster with the combination of treatments [62,63]. Overlearning is a behavioral intervention that is not begun until the child has been successfully dry with the alarm for at least 2 weeks. At this point, the child is asked to drink about 500 mL of water during the hour before going to bed. The child continues to use the alarm until he or she is dry for 14 consecutive nights with the extra fluid intake. Overlearning has consistently been found to decrease the relapse rate after alarm treatment. Young and Morgan [64] found that use of the overlearning procedure decreased the relapse rate from 29% to 10%. Houts and colleagues [65] found that the relapse rate 3 months after treatment decreased from 50% to 11% with the overlearning procedure.

Multicomponent behavioral interventions

Although overlearning is helpful in preventing relapse, in general, adding a single behavioral intervention to the enuresis alarm has not been shown to improve initial efficacy consistently; therefore, multicomponent behavioral interventions have been developed in an attempt to improve outcome. Two multicomponent interventions that have been the subject of multiple studies—dry-bed training and full-spectrum home training—are discussed herein.

Full-spectrum home training is a manual-guided behavioral treatment that incorporates the enuresis alarm with retention control training, overlearning, and cleanliness training [65]. Cleanliness training requires that, at each episode of bed-wetting, the child take primary responsibility for changing wet clothes and bed linens, remaking the bed, and resetting the alarm. Initial success rates with full-spectrum home training have ranged from 60% to 80%, which is not superior to initial success with the alarm alone [62,66]. Some evidence suggests that improvement may be somewhat more rapid with this treatment package than with the alarm alone, but this difference has not been convincingly demonstrated. As one might expect with the inclusion of overlearning in the package, relapse rates are generally lower than with the alarm alone [62].

Dry-bed training involves some of the procedures described previously but also has many unique features (for a full description see the article by Azrin et al [67]). It begins with an intensive first night of training that involves increased fluid consumption, hourly awakenings, praise when the bed is dry at the awakenings, and, when the alarm goes off, a mild reprimand and cleanliness training. In addition, before going to bed and after any episode of wetting, the child is required to engage in 20 practice trials of appropriate toileting (eg, positive practice). For each practice trial, the child lies in bed, counts to 50, arises and attempts to urinate in the toilet, and then returns to bed. After the first night, the intervention continues to include the enuresis alarm, positive practice, cleanliness training, reprimands for wetting, and praise for dry nights. Night wakings are decreased to one per night, usually about 3 hours after the child has gone to bed. After a dry night, the night waking time is moved 30 minutes earlier; it is discontinued when it is scheduled to occur 1 hour after the child's bedtime. After 7 consecutive dry nights, the alarm is discontinued but may be reinstituted if two episodes of bed-wetting occur in a 1-week period. Initial success with dry-bed training ranges from 67% to 100%. The 100% figure has been reported in more than one study and by more than one research group [67–70]. When dry-bed training has been compared with the enuresis alarm alone, there is a consistent trend toward studies reporting higher initial success rates with dry-bed training, although the differences are not always statistically significant [68,70,71].

Use of the enuresis alarm in combination with desmopressin

The frequent night awakenings and the slow onset of action are two of the more common concerns about treatment with the enuresis alarm.

In contrast, as described elsewhere in this issue, desmopressin has a rapid onset of action and often decreases the frequency of wet nights, but only a minority of children are consistently dry at night on desmopressin, and, when the medication is stopped, relapse rates are much higher than with the alarm. The differing characteristics of the two interventions have led to interest in the effect of combining them. Potentially, the combined intervention may result in a more rapid onset of action and less frequent night wakings than with the alarm alone, but lower relapse rates than with desmopressin alone.

Not surprisingly given the use of desmopressin, studies have found that the combined intervention does result in an increase in dry nights early in the intervention [72,73]. One study has suggested a better overall response rate in children treated with the combination therapy, but the alarm only group was not given a placebo [74]. Two placebo-controlled trials have not found any long-term benefit of combining the alarm with desmopressin [73,75]. Although these studies suggest that, for most children, the combination of the alarm and desmopressin has little benefit over the alarm alone, the possibility remains that some children may do better with the combination. For example, if a child is regularly wetting more than once a night, the alarm will not be tolerable for many families. If desmopressin decreases the frequency of wetting to about once a night, it is possible that the alarm may be better tolerated and more effective. Further studies are needed to determine if there are subsets of children or desmopressin-dosing strategies that may result in improved outcome with the combination therapy when compared with the alarm alone.

Hypnotherapy

Hypnotherapy is a treatment modality in which a patient is induced to enter a hypnotic or trance state, followed by implementation of a treatment with the individual in that state. For nocturnal enuresis, the treatment usually involves the suggestion during the trance that the child will wake up if he or she needs to urinate during the night, that their bed will be dry in the morning, that their bladder will be able to hold more urine, and that the child will be able to control when he or she urinates [76–78].

Case series suggest that 60% to 70% of children with nocturnal enuresis can be cured with the combination of hypnosis and suggestion [77,78]. Olness [78] found that 70% of 40 children taught to use self-hypnosis before going to bed each night ceased wetting the bed within the first month of treatment and with no more that two treatment sessions. In a clinical trial, Banerjee and colleagues [76] compared a minimum of three 30-minute sessions of hypnotherapy with treatment with imipramine. The initial responses to hypnotherapy and imipramine were comparable, but 6 months after the cessation of treatment, 68% of the hypnotherapy group was significantly improved versus 24% of the imipramine-treated group. In that study, children older than 7 years were found to have a better response to hypnotherapy than younger children.

The mechanism by which hypnotherapy treats enuresis is not well understood. One clinical trial found that suggestions without the induction of a trance were as effective as suggestions in the presence of a trance, with both groups showing a significantly greater decrease in wet nights than a wait-list control group [79]. It seems likely to be important that clinicians convey a positive hopeful approach that instills in the child and family the belief that they can be successful. Hypnotherapy with positive suggestions seems to be a promising treatment, although this view has been questioned by some [80]. Clearly, further studies are needed to delineate how best to use this method in the armamentarium of available treatments for nocturnal enuresis.

Acupuncture

Several published large case series from China suggest that acupuncture may be an effective treatment for nocturnal enuresis. Chunpu [81] reported a 98% cure rate in 500 children, most of whom were treated with one or two 30-minute sessions, and Baoqin [82] reported a 73% cure rate in over 300 children with 10 to more than 40 sessions of acupuncture. Smaller studies from other countries have also reported positive results. Serel and colleagues [83] treated 50 children with more than 60 sessions that were 30-minutes in length and reported that 86% of the children were completely dry after 6 months, whereas Bjorkstrom et al [84] found that only 22% of the 25 children they treated had more than a 90% reduction in wet nights. One randomized trial compared acupuncture with desmopressin and found similar response rates [85]; however, when the response rates were measured 6 months after the end of treatment, 75% of the desmopressin group compared with 65% of the

acupuncture group were reported to be dry at night. These findings suggest a much higher long-term response rate to desmopressin than the 5% to 20% rate reported in most other studies [86], leading one to question whether the results of this study can be generalized to other children with nocturnal enuresis. Case series suggest some promising results, but studies comparing the intervention group with a control group or the enuresis alarm are needed. In addition, the reasons for the large heterogeneity in how the intervention is administered, particularly the number of treatment sessions, need to be elucidated.

Summary

Nocturnal enuresis is a heterogeneous disorder that is stressful for children and families. Most children with primary enuresis do not have clinically significant behavior problems or decreases in self-concept, but when these problems are present, successful treatment is likely to have some benefit. On the other hand, repeated treatment failures may be detrimental. Of the available behavioral treatments, the enuresis alarm has the best-documented efficacy. Overlearning can decrease the relapse rate when alarm treatment is stopped, but it is not clear that any other single behavioral intervention improves the alarm's initial efficacy. Dry-bed training may be somewhat more effective than the alarm alone, but significant training and support of the family may be needed to carry out this demanding procedure. Hypnosis and acupuncture are potentially useful interventions that require further study.

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The adolescent varicocele: to treat or not to treat

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A *varicocele* is a dilatation of the testicular vein and the pampiniform venous plexus within the spermatic cord. Although rare in pediatric populations, the prevalence of varicoceles markedly increases with pubertal development to approximately 15% by the late teenage years, a rate similar to that in adult populations [1,2]. Varicoceles are progressive lesions that may hinder testicular growth and function over time and are the most common and correctable cause of male infertility. The incidence of varicocele in men with abnormal semen is 25% compared with almost 12% in men with normal semen [3]. Approximately 40% of men with primary infertility have a varicocele, over half of whom experience improvements in semen parameters following varicocelectomy [4–6]. The rate at which varicoceles develop, however, and the severity of testicular injury leading to infertility, are highly variable and time-dependent.

The decision to treat adolescents with varicocele is controversial because over 80% of adult varicoceles are not associated with infertility [3]. Most physicians agree that treating all adolescents with varicocele—thus subjecting a large percentage of boys to unnecessary surgery—is inappropriate, costly, and not without ethical considerations. Waiting until patients present as adults with potentially irreversible infertility, however, is equally unacceptable. The task for pediatricians and urologists is to determine which adolescents are at greatest risk for future fertility problems and warrant early intervention. This article reviews the current literature surrounding adolescent varicocele and offers recommendations for identifying individuals who would most benefit from treatment.

Anatomy and varicocele formation

The formation of varicocele has been attributed predominantly to anatomic variance, increased pressure in the left renal vein, and incompetent or congenitally absent valves. Approximately 90% of varicoceles are unilateral left-sided. Several anatomic differences between the right and left testicular (internal spermatic) veins are believed to contribute to this predominance. Although highly variable, the left system usually consists of one or more veins within the spermatic cord that coalesce in the retroperitoneal space to become the testicular vein. The left testicular vein inserts into the left renal vein at a right angle, whereas the right testicular vein joins the inferior vena cava at an oblique angle. The relative greater flow of the inferior vena cava is thought to augment drainage on the right [7]. The left testicular vein, however, is 8 to 10 cm longer (more craniad) than the right, with a proportional increase in pressure head.

Increases in left renal vein pressure also have been noted secondary to two *nutcracker phenomenon* mechanisms [8]. The *proximal* "nutcracker" describes compression of the left renal artery as it passes between the aorta and superior mesenteric arteries. The *distal* mechanism involves retrograde blood flow through the deferential and external spermatic veins caused by compression of the left common iliac vein as it courses under the left common iliac artery.

Congenitally absent or incompetent valves classically have been taught as the primary etiology of varicocele formation. Subsequent research has shown that there are males without varicocele

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who have incompetent or absent testicular vein valves and males with varicocele who have competent valves [9,10]. Even with normal valves, dilation of the testicular vein can cause functional incompetence as a result of loss of coaptation [11]. Valve pathology may not be a sole cause, but it certainly contributes to varicocele formation and severity.

Pathophysiology of testicular dysfunction

Presence of clinically detectable varicocele is associated with testicular hypotrophy, an abnormal gonadotropin axis, histologic changes, abnormal spermatogenesis, and infertility. How the varicocele exerts toxic effects on the testicle is not known precisely. Many theories have been postulated, including increased testicular temperature, hypoxia, reflux of adrenal and renal metabolites, and generation of reactive oxygen species.

Hyperthermia of the scrotum and testes is the most widely accepted mechanism for testicular dysfunction. Experimentally induced varicocele increases scrotal temperature and is reversible with surgical correction [12,13]. Varicocelectomy in human studies also shows similar normalization of temperature with subsequent increases in sperm count [14,15]. Compared with infertile men with varicocele, there is a significant decrease in intrascrotal temperature in normal controls as well as men with varicocele and normal fertility [16,17]. Increased scrotal temperature in turn alters cellular metabolism and enzymatic function, and induces apoptosis in germ cells [18–20].

Studies have not supported the proposal that venous stasis and reduced blood flow of the testicular vessels result in hypoxia. Analysis of testicular blood gases and pH in men with varicocele show no significant difference compared with controls or relationship to impaired spermatogenesis [21–23].

Reflux of adrenal and renal metabolites has been proposed as a mechanism for testicular damage in men with varicocele. Research has been inconclusive and experimental studies have shown that toxic effects of varicocele do not require adrenal contribution and that reflux may not occur [24]. Adrenomedullin, a potent vasodilator expressed in adrenal and kidney tissues but not in the testes, has been isolated in blood samples from the testicular veins of men with varicocele [25]. Further research is required to determine if adrenomedullin plays a role in formation of or toxicity associated with varicocele.

Venous blood from varicoceles of infertile men demonstrates increased production of nitric oxide, its active metabolites, and reactive oxygen species that are known to play a role in sperm dysfunction [26–28]. These increased levels correlate with severity of varicocele [27]. Varicocele also reduces antioxidant defenses, potentially adding to the localized oxidative stress [29]. Both of these trends are reversed significantly following varicocelectomy [30]. This proposed mechanism of testicular toxicity could explain why bilateral dysfunction is seen in many men with unilateral varicocele because nitric oxide freely diffuses across membranes. Whether this mechanism is the final common pathway for varicocele-induced infertility or an effect of testicular injury is unknown. No report has been published investigating the role of antioxidant therapy in adolescent or adult varicocele.

Diagnosis

Typically, varicoceles are asymptomatic and detected in adolescents during routine physical examination. Occasionally, scrotal mass evaluations that are referred from primary care physicians are found to be varicoceles. Differential diagnoses for generally painless scrotal masses in adolescence include communicating hydrocele, hydrocele of the spermatic cord, inguinal hernia, epididymal cyst, and spermatocele.

Patients should be examined in a warm room in standing and supine positions, and with and without a Valsalva maneuver. Classically, varicoceles are graded according to the following criteria:

Grade I (small): Palpable only with Valsalva maneuver
Grade II (medium): Palpable with patient standing
Grade III (large): Visible through scrotal skin, palpable with patient standing

After examining the patient in upright position, he should be re-examined in the supine position. Idiopathic varicocele is more prominent in the upright position and disappears in the supine position. Secondary varicoceles, especially on the right side, can be caused by retroperitoneal tumors or lymphadenopathy and do not change size as noticeably in the supine position.

An important part of the physical examination in all boys with varicocele is an accurate assessment of testicular consistency (firmness) and volume. Although the assessment of testicular

consistency is subjective, a careful simultaneous comparison of both testes may give the clinician additional qualitative information about the overall condition of the ipsilateral testis. Several methods are available to measure the size of the testis, including visual comparison, calipers, Prader orchidometer (comparative ovoids), Takahira orchidometer (disk elliptical rings), and ultrasound. Measurement of testis volume reportedly is assessed accurately and reproducibly by using either a Prader or disk orchidometer [31]. Ultrasound should be considered the criterion standard for assessing testicular volume, however. It consistently has shown high correlation with actual testis volume and has been highly reproducible.

In a clinical study comparing Prader orchidometer and ultrasound in adolescents with a varicocele, Costabile and colleagues [32] found that 24% of patients with growth arrest would have been missed and 14% would have been identified falsely to have a significant size discrepancy if measured by Prader orchidometer alone. Diamond and colleagues [33] noted similar superiority of ultrasound for measuring testicular volume; they recommend annual ultrasound assessment of testis in adolescents with varicocele.

Pathologic effects of varicocele

In adults, the toxic effects of varicocele may cause semen abnormalities and histopathologic changes. The most common findings on semen analysis are decreased motility, decreased sperm density, and increased number of pathologic sperm forms [3,34]. Histologic studies from testicular biopsy in males with varicocele reveal Leydig cell hyperplasia, decreased number of spermatogonia per tubule, decreased spermatogenesis and maturation arrest, sloughing of germinal epithelium, and interstitial fibrosis [35,36]. Because the adult testicle is comprised mostly of seminiferous and germinal cells, it is not surprising that decreases in testicular volume directly correlate with testicular function as measured by semen analysis [37,38].

The toxic effect of varicocele on semen parameters has been demonstrated in adolescents [34]. The correlation between testicular hypotrophy and abnormal spermatogenesis in this age group, however, is less evident. Haans and colleagues [39] reported that adolescents with pronounced left testicular growth failure had significantly reduced sperm count, but concentration, motility, and morphology were unaffected. A recent article examined 76 Tanner stage–V adolescents and separated them into two groups: those with pathologic semen analysis and those with normal semen. Although there was a reduction in mean left testicular volume among those with abnormal semen (18.2 mL versus 20.5 mL) it was not statistically significant [38]. This lack of clear association in adolescents can be explained in part by the fact that left testicular growth failure occurs before significant decreases in semen parameters and the time between varies highly. Furthermore, such data may not need to be demonstrated in adolescents given the direct correlation between testicular volume and spermatogenesis reported in the adult literature.

Identifying those at risk

Left untreated, with time the varicocele will continue to affect testicular growth with loss of volume and progressive deterioration in semen parameters [19,40]. In adults, the indication for treatment is straightforward because the criteria have been established already, with 12 months of infertility with abnormal semen analysis and the presence of varicocele. In the adolescent, a converse situation exists. The diagnosis of varicocele leads to additional questions about possible infertility and the need to establish clinical criteria for varicocele repair. Currently, the clinical tests for identifying "at risk" adolescents with varicocele include (1) physical examination, (2) biochemical evaluation, and (3) semen analysis.

Physical examination

Physical examination includes the varicocele grade and the measurement of testicular volume. There are conflicting opinions about the correlation between the grade of varicocele and its ultimate effect on the testis. Some investigators have found no correlation between varicocele grade and testicular size, whereas others have noticed that boys with severe varicoceles have smaller ipsilateral testis [32,41]. In an early study involving adolescent boys and young men 12 to 25 years of age, 34% of subjects with a grade-II varicocele had testicular changes, compared with 81% of those with grade-III varicocele. Within the grade-III group, the percentage of subjects 18 to 25 years of age with testicular change reached almost 98%, illustrating the progressive nature of varicocele-induced testicular damage and indicating that testicular hypotrophy is almost inevitable in males

with grade-III varicocele [42]. Although the higher-grade varicoceles seem more concerning, varicocele grade should not be a sole determinant in recommending treatment.

There is abundant literature confirming that varicocele is associated with testicular growth arrest in adolescents, and varicocele repair results in testicular "catch-up" growth [43–46]. The risk for testicular growth arrest also has been shown to correlate with varicocele size and increase with time [47,48]. There is no clear proof, however, that later fertility problems will be averted in these boys because the relationship between testis size and semen quality has not been defined precisely. Therefore, additional tests are needed that would differentiate better between boys who will develop infertility and those who will remain fertile.

Biochemical tests

Biochemical tests are based on the integrity of the testis and any effect of the varicocele on the hypothalamic-pituitary axis. At the testis level, serum *inhibin* levels reflect the integrity of the seminiferous tubules and the function of Sertoli cells. There are not enough data to support the use of serum inhibin levels in stratifying adolescents with varicoceles [49,50].

Gonadotropin-releasing hormone (GnRH) stimulation test is based on the theory that damage to germinal epithelium results in compensatory stimulation of the pituitary gland and subsequent increase in follicle-stimulating hormone (FSH) and luteinizing-hormone (LH) production by gonadotrophs. Several studies demonstrate an abnormal gonadotropin axis in men with varicocele as evidenced by increased FSH or LH response to administration of GnRH [49,51,52]. An abnormal gonadotropin response represents some degree of testicular injury, and it has been suggested that GnRH stimulation could be used for evaluation of testicular function in adolescents. Gonadotropin abnormalities, however, have been observed in fertile as well as infertile adult men with varicocele [53]. In adolescents, the relationship between an abnormal or normal test result and future fertility remains unclear [54].

Semen analysis

Semen analysis in men with varicoceles reveals decreased motility, decreased sperm density, and more pathologic forms. By applying strict morphologic criteria to semen analysis, varicocele repair improves the seminal parameters in approximately 70% of patients with the improvement in motility being the most common [46,55].

Few studies have evaluated semen quality in adolescents with varicoceles, most likely because of ethical concerns in the procurement of semen specimens in young patients [39,43,56]. In addition, there are no established norms for adolescent semen analysis [34]. In a study of 88 boys, Laven and colleagues [43] found a statistically significant increase in sperm concentration values 1 year after varicocele repair. No differences in total sperm count, sperm motility, or morphology were observed among postoperative varicocele patients, normal healthy boys, and in controls with untreated varicoceles.

Management

Prophylactic surgery for every adolescent with varicocele is not advisable. Understanding the limitations in predicting future fertility potential, however, several reproducible parameters would be helpful in identifying individuals who would benefit most from treatment. Testicular volume discrepancy of more than 2 mL as assessed by ultrasonography is the most common indication for treatment. The authors prefer to follow testicular volume with ultrasound. Several studies, however, have demonstrated a strong linear relationship between testicular volume measurements using either Prader orchidometer or scrotal ultrasound [39,57,58]. It is recommended that the clinician use the method with which he or she has the most experience.

Symptoms such as pain, fullness, or swelling not relieved by conservative measures should be another possible indicator for treatment. Because it would be difficult to have a "normal" contralateral testis as a comparison, adolescents with bilateral varicoceles should be considered for therapy. For the older adolescent, the physician may discuss the possibility of semen analysis to aid in decision-making. A patient with abnormal semen analysis with high-grade varicocele, even without testicular hypotrophy, should be considered for treatment.

Treatment options

The best method for treatment of adolescent varicocele has yet to be established. There have been no randomized, controlled, prospective clinical studies that compare the various techniques in adolescents or adults. Treatment options include

open surgical approaches, laparoscopic varicocele ligation, and embolization. Depending on the methods, the recurrence of the varicocele after the repair can occur in 9% to 16% of adolescents.

Open surgery remains the mainstay of varicocele treatment in adolescents. Based on a review of the literature and the results of a survey of pediatric urologists in the United States, Paduch and Skoog [46] found that high retroperitoneal ligation of the testicular artery and veins (Palomo) is the treatment of choice in adolescents. Kass and Marcol [59] demonstrated that the classic Palomo repair was associated with a statistically significant decrease in surgical failure rate compared with artery sparing or inguinal varicocele ligation. In addition, no patient exhibited testis atrophy after high ligation of internal spermatic artery and vein, which is consistent with findings by other investigators [56,60].

The issue of preserving the testicular artery has been questioned in adults, where inadvertent arterial ligation during inguinal dissection for varicocele ligation led to poorer postoperative sperm quality compared with artery-preserved cohorts [44]. Microscopic inguinal or subinguinal approach with arterial preservation also should be considered as viable options for adolescent varicocele treatment. The microsurgical low inguinal or subinguinal approach has been reported in the adult infertility literature as the method with the highest success rate (99%) and the lowest morbidity (0% hydrocele). Its main disadvantage is the need for an operating microscope to spare the arteries and lymphatics and the increased number of veins at this level. The laparoscopic repair is an artery-sparing approach but includes intra-abdominal risks. Its other disadvantage is the cost-effectiveness of the instruments and the surgical time for a unilateral repair. Transvenous varicole ablation has the advantages of a quick recovery and minimal pain. The success rate ranges from 89% to 95% with approximately 6% complications, in addition to the issue of radiologic exposure of the testes. Many urologists reserve this approach for cases of surgical failure [61].

The future

There is a great need for further research to improve selection of patients who need surgical correction of varicocele. Advanced molecular biology techniques used for evaluation of the infertile male have increased understanding of the physiology of spermatogenesis. It is estimated that 13% of males with azoospermia carry microdeletions of the long arm of chromosome Y [62–64]. Males with varicocele and azoospermia or severe oligoasthenospermia may suffer from point mutation or deletion of genes important in spermatogenesis. Y-chromosome microdeletion analysis is not universally available and the assay technique has not been standardized fully. In the near future, by screening for aberrations of genes involved in regulation of spermatogenesis, better criteria for management of patients with varicocele may be established [46,55].

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Urinary tract infection in children: etiology and epidemiology

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Although the urinary tract is a common source of infection in children and infants, the implications of urinary tract infections (UTIs) in children and infants are different from those in adults. These differences are reflected in the bacteriology, pathogenesis, and epidemiology of UTI. The importance of the various pathogenic mechanisms of UTI is reflected in the bacteriology. Although retrograde ascending infection is probably the most common pathway, seeding from systemic and nosocomial infection is a significant pathway to infection in infants and immunocompromised children.

Bacteriology

The common pathogenic sources of UTI are bacteria of enteric origin, although other pathogens (fungi, mycobacteria, and viruses) also are encountered. In neonates, group B streptococci urinary infection is more common than in older children and adults, perhaps reflecting the colonization status of the mothers and that infants may be more subject to infection from systemic seeding. During the rest of childhood, *Escherichia coli* is the most frequent culprit for all mechanisms of UTI, including nosocomial causes, although other bacteria may be found (Box 1). *Lactobacillus* spp, coagulase-negative staphylococci, and *Corynebacterium* spp are not considered pathogens in otherwise healthy children 2 months to 2 years of age [1].

The arrival of pathogens in the urinary tract of a healthy child is usually the result of retrograde migration of enteric bacteria colonizing the periurethral area, and reflects this flora. On the other hand, in an immunocompromised individual, more unusual and opportunistic pathogens also may be involved. In patients with AIDS, *Escherichia coli* is still the most common pathogen, although *Streptococcus faecalis (Enterococcus)* is encountered more frequently than in healthy people [2].

UTI is a common nosocomial infection in hospitalized patients [3]. *Escherichia coli* (19%), *Candida albicans* (14.3%), and *Pseudomonas aeruginosa* (13.1%) are the most common pathogens associated with nosocomial UTI [4]. Hematogenous seeding of the urinary tract during sepsis by pathogens such as S*taphylococcus aureus* or urosepsis resulting from urinary tract obstruction also occurs.

Viral UTI is more common in immunocompromised patients, particularly those receiving immunosuppressants, than in otherwise healthy children. Adenovirus and BK virus are viral pathogens that may cause hemorrhagic cystitis [5,6].

Pathogenesis

The human urinary tract is a unique space lined with mucosa (transitional cells). Unlike the gastrointestinal (GI) tract, it is usually a sterile space with an impermeable lining. UTI occurs with entrance of pathogens into the urinary tract and subsequent adherence to it. Although normal voiding with intermittent urinary outflow usually clears pathogens within the bladder, human urine

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Box 1. Urinary pathogens

Gram-negative rods
Citrobacter spp
Escherichia coli
Enterobacter spp
Gardnerella vaginalis
Klebsiella spp
Morganella morganii
Proteus spp
Providencia stuartii
Pseudomonas aeruginosa
Serratia spp

Gram-negative cocci
Neisseria gonorrhea

Gram-positive cocci
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus saprophyticus
Streptococcus group D
Streptococcus faecalis
Streptococcus bovis
Streptococcus group B

Other pathogens
Candida albicans
Chlamydia trachomatis
Ureaplasma urealyticum

Data from Chon HC, Lai FC, Shortliffe LD. Pediatric urinary tract infections. Pediatr Clin North Am 2001;48:1441–59.

has enough nutrients (eg, amino acids, glucose) for bacterial growth. Moreover, when abnormal voiding with residual urine or bacterial adherence occurs, mechanical clearance by voiding may be inadequate, and UTI may result.

There are three mechanisms through which the urinary tract may become infected: (1) retrograde ascent of fecal-perineal bacteria, (2) nosocomial or bacterial introduction in a medical setting through instrumentation, and (3) urinary tract involvement as part of a systemic infection (Fig. 1).

The most common mechanism is retrograde ascent. The bacteria associated with retrograde ascent most often come from the host's bowel. The transfer of pathogens from the bowel into the urinary tract occurs through vaginal or periurethral colonization. Once entrance into the urinary outlet occurs, pathogens may enter the urinary tract given certain risk factors. These factors often

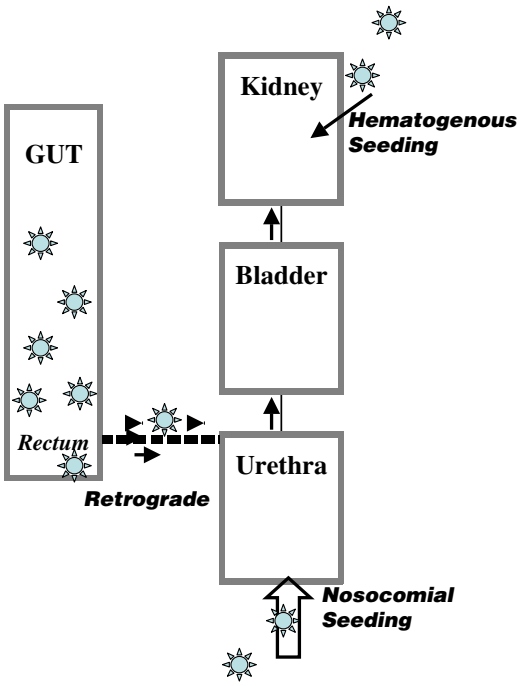

Fig. 1. Major pathways of pathogen spreading in urinary tract infection.

relate to bacterial or host characteristics that allow increased susceptibility to bacteriuria by way of increased bacterial adherence to the epithelia.

Many urinary pathogens possess fimbrial or nonfimbrial adhesins (type-1 fimbriae and P fimbriae) for introital and periurethral or mucosal adhesion, and subsequent colonization [7]. Type-1 fimbriae bind to mannose-containing receptors, and the interaction can be blocked by free mannose. The pathogens with type-1 fimbriae are *mannose-sensitive*. Mannose-sensitive *Escherichia coli* is found more often than other *Escherichia coli* strains in acute cystitis [8]. Recently, the receptors of type-1 fimbriae have been identified as *uroplakins*, a group of glycosylated proteins forming a layer of matrix on the surface of urothelium [9]. P fimbriae bind to Galα(1–4)Gal moiety of the P blood group, which is distributed widely on the urothelial mucosa. Mannose does not block the binding process; therefore, the bacteria with P fimbriae are *mannose-resistant*. P-fimbriated *Escherichia coli* strains are associated strongly with acute pyelonephritis, probably because the major glycolipid components of renal cells are receptors for P fimbriae [10].

Once attached to the surface of urothelial mucosa, the bacteria can switch the expression of

different fimbriae to maximize their survival advantage. The expression of type-1 fimbriae is determined by various external factors such as temperature, nutrients, and growth conditions [11]. The expression of P fimbriae also can be switched on and off according to the availability of nutrients [12]. Once the adherence and ascendance in the urinary tract occur, successful infection requires quick multiplication. Multiple bacterial mechanisms that optimize growth or increase virulence are understood incompletely. Some, for instance, manipulate urinary acidity with urease, or activate iron-scavenging protein expression [7]. Environmental regulation of virulence factors such as bacterial toxin production is being examined. Factors such as osmolarity, temperature, and anaerobic condition may regulate the expression of alpha-hemolysin in *Escherichia coli*, which in turn may be important during renal invasion [13].

Virulence factors seem to be transferred from bacteria to bacteria through DNA exchange involving "pathogenicity islands," large regions of DNA up to 200 kilobase (kb) long. The interbacterial transfer probably is mediated by bacterial phages, which are bacterial viruses [14]. This phenomenon is similar to the DNA transfer that occurs between bacteria with transferal of antibiotic-resistant genes. Further investigation will allow better understanding of the roles of the virulence factors in establishing and maintaining UTI.

The second mechanism is the introduction of pathogens by way of a foreign body or instrument. Urinary infection is the third most common nosocomial infection after primary bloodstream infections and pneumonia in intensive care units [4]. A recent prospective study estimates the incidence of nosocomial UTI as 0.6 case/1000 patient/day, and newborns and infants are affected disproportionately [15]. The infection is associated frequently with urethral catheterization.

Finally, infants, young children, and some immunocompromised individuals may have gram-positive bacteriuria that may be caused by urinary tract seeding from a systemic infection. More fastidious organisms such as *Mycobacterium tuberculosis* or viruses also may gain access by this route.

Classification

The classification of UTI is complex for historical reasons, and many classification systems exist. UTI can be classified by the sites of infection (bladder [cystitis], kidney [pyelonephritis]), or by severity (complicated versus uncomplicated). For practical purposes, the authors categorize pediatric UTI as either *first* or *recurrent* based on the natural history because this may affect clinical management. The recurrent UTI can be subcategorized further as (1) unresolved bacteriuria, (2) bacterial persistence, or (3) reinfection [16].

The first infection is the initially diagnosed UTI. In infants and children the first infection is complicated because of the potential association with anatomic anomalies. A high prevalence of anatomic anomalies occurs in children and may predispose them to complications of UTI and potential renal damage. Unresolved infection may result from subtherapeutic level of antimicrobial agent from noncompliance, malabsorption, or inadequate drug metabolism, or the presence of resistant pathogens unresponsive to current treatment. In these situations, correcting antimicrobial dose or switching to a more appropriate drug cures the UTI.

Bacterial persistence is different from unresolved infection. In this case there is a nidus for persistent infection that cannot be eradicated. As a result, the same pathogen is identified in recurrent infections, but episodes of sterile urine may occur during and shortly following antimicrobial treatment. Bacteria reside in an isolated portion (or anomaly) of the urinary tract where the pathogens are shielded from the current treatment, resulting in a persistent nidus of infection (*eg*, infected staghorn stones). The treatment options are more complicated and often require surgical correction of underlying abnormalities with extirpation of the nidus.

By definition, reinfection differs from bacterial persistence because each episode is a new infection, freshly acquired from periurethral colonization and the perineal and rectal flora. Confusion in this form of pathogenesis sometimes occurs because *Escherichia coli*, the most common general pathogenic species, occurs in many different serotypes; thus, recurrent *Escherichia coli* UTI does not equate to infection with the same organism. With serotyping, reinfection can be established, but this is done rarely in the routine clinical setting.

To urologists, the surgically correctable abnormalities of urinary tract are particularly important. These abnormalities may predispose a subset of children to recurrent UTI with potential ultimate complications of renal scarring and function deterioration (Box 2). These risk factors can be extirpated surgically, and the contribution of surgical correction may be superior medical management in the overall care of children with UTI.

Box 2. Surgically correctable causes of bacterial persistence in children

Infection stones
Infected nonfunctional renal segments
Infected ureteral stumps after nephrectomy
Vesicointestinal or urethrorectal fistula
Vesicovaginal fistula
Infected necrotic papillae in papillary necrosis
Unilateral medullary sponge kidney
Infected urachal cyst
Infected urethral diverticulum or periurethral glands

Data from Shortliffe LD. Urinary tract infection in infants and children. In: Walsh P, Retik AB, Vaughn ED, Wein AJ, editors. Campbell's urology. 8th edition. Philadelphia: Saunders; 2002, p. 1846–84.

Box 3. Host factors affecting bacteriuria

Age
Gender
Colonization
  Periurethral
  Preputial
  Fecal
  Vaginal
Genetics (urothelial receptors)
Renal scarring
Native immunity
Genitourinary abnormalities
  Vesicoureteral reflux
  Pregnancy
  Neurogenic bladder
Iatrogenic factors

Data from Shortliffe LD. Urinary tract infection in infants and children. In: Walsh P, Retik AB, Vaughn ED, Wein AJ, editors. Campbell's urology. 8th edition. Philadelphia: Saunders; 2002, p. 1846–84.

Epidemiology and risk factors

Factors that seem to affect the incidence of UTI are associated with gender, age, race, circumcision status, and general health or immune status. Host factors that contribute to increased bacterial adherence seem to be associated with age, gender, and colonization. Increased periurethral colonization, whether age-related (eg, infancy), or individual (eg, the increased colonization associated with those who have recurrent UTI or uncircumcised infants) seems to confer increased risk for UTI. Structural abnormalities, neurologic deficiency, or behavioral voiding dysfunction resulting in residual urine in any part of the urinary tract also may influence the persistence of bacteriuria once established. Hosts also have certain characteristics, listed in Box 3, that make them more vulnerable to bacteriuria [17].

Regardless of age (except perhaps for the neonatal period), girls are more vulnerable to UTI than boys are. Approximately 3% of prepubertal girls and 1% of prepubertal boys are diagnosed with UTI (Table 1) [18,19]. In febrile young children UTI is common, with incidence usually 3% to 5%, and up to 13.6% in one prospective study [20,21]. The relative risk for UTI in febrile girls to boys 2 months to 2 years of age is 2.27 [1]. In a prospective, multi-centered study in Sweden, however, the incidences of UTI in boys and girls younger than 2 years of age are the same (1.6%) [22].

In older children, particularly in sexually active teenagers, there is a female predominance of UTI, probably as a result of sexual activities or the use of birth control. A recent prospective study of sexually active young women reveals asymptomatic bacteriuria rate at 4% to 6%, and only 8% of the women with bacteriuria develop symptomatic UTI [23].

Race seems to affect the incidence of UTI. In developed countries with adequate medical resources, UTI is more common in white girls than

Table 1
Incidence of urinary tract infection in children

Age	Girls	Boys
Infancy	0.4%–1%	0.188% (uncircumcised) 0.702% (circumcised)
1–5 y	0.9%–1.4%	0.1–0.2%
School age	0.7%–2.3%	0.04–0.2%
Overall incidence	3%	1%

Data from Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Am J Med 2002;113(1A):5S–13S.

girls of other races [20,24,25]. Although UTI occurs in children of all races and ethnicities, the incidence is low in African-American children [25].

Although certain individuals are more prone to UTI, no specific genes are linked yet to UTI [26]. The secretor status, as determined by hemagglutination inhibition assay in saliva, has been linked to increased risk for pyelonephritis, but not to sporadic UTI [27,28]. The deficiencies of interleukin-8 receptor, neutrophil-mediated, and chemokine receptor (CXCR1) also seem to increase the risk for UTI in experimental models [29,30].

In infant boys neonatal circumcision is associated with a decreased risk for UTI (from 0.702% to 0.188% in a cohort study) [31]. Two other prospective studies comparing circumcision in boys with a history of UTI also provide evidence that circumcision decreases the risk for symptomatic UTI and bacteriuria in this population, with a protective effect that may be independent of age [32,33]. There is also evidence that circumcision is associated with lower risk for epididymitis in boys [34,35].

Neonates and infants are at higher risk for UTI, which coincides with their incompletely developed immunity. In particular, secretory IgA may be deficient until after 1 year of age. Children who receive breast milk have higher IgA levels than nonbreastfed children [36]. Breast milk seems to protect children from UTI and other infections (eg, respiratory infections, otitis media, necrotizing enterocolitis, and neonatal septicemia), perhaps from the protective effect of maternal IgA against the mucosal invasion of pathogens [37,38].

Diabetes mellitus increases the risk for UTI in patients of all ages [39]. In the past, pediatric diabetes mellitus was mostly type 1 (primary islet-cell hyposecretion of insulin). Now, type 2 diabetes mellitus (insulin-receptor insensitivity) is no longer only an adult disease, probably because of increased pediatric obesity [40]. Diabetic patients also suffer more severe UTI complications, such as emphysematous cystitis, pyelonephritis, and fungemia [41]. Clinicians need to be vigilant in monitoring these children.

In immunocompromised patients, UTI is more common and has more severe sequelae. Hospitalizations for septicemia were associated most commonly with UTI as a secondary diagnosis after renal transplantation surgery [42]. In a retrospective study of bacteremia in pediatric HIV-positive patients, UTI is the second most common cause of bacteremia after pneumonia [2,43]. The risk for UTI is correlated with the clinical progression of HIV infection. Although fewer data are available in children, in a study of adult men with AIDS, bacteriuria is more common in those with diagnosed AIDS (13.3%) than those with asymptomatic HIV infection (3.2%) and those without HIV infection (1.8%). Symptomatic UTI was found only in patients with AIDS, not in patients of the other two groups [44].

Many children have recurrent UTI after the initial infection. Most recurrences occur after 3 to 6 months. The rate of recurrence is 18% in boys, and 26% in girls before 1 year of age. The rate of recurrence increases to 32% in boys older than 1 year of age. In girls older than 1 year of age, the risk for recurrence is proportional to the number of previous infections [45].

In the past decade, with improved understanding of pathogenesis and more vigorous prevention, the incidence of nosocomial UTI in children has decreased from 0.9 case/1000 patient/day to 0.6 case/1000 patient/day [15].

Symptoms and findings associated with urinary tract infection

The classic presentations of dysuria, frequency, hesitancy, and flank pain in adults are unreliable when applied to pediatric UTI, particularly in infants. The presenting complaints in children tend to be vague, including fever, irritability, lethargy, poor feeding, failure to thrive, nonspecific GI complaints, and incontinence. Fever is the most common presentation in young children. In one study, 5.3% of all emergency room visits for fever in infants were diagnosed with UTI [46]. For this reason, the American Academy of Pediatrics (AAP) recommends UTI be ruled out in any child 2 months to 2 years of age with unexplained fever [1]. Even when signs point to another source of infection, UTI still needs to be ruled out because those not suspected to have UTI are equally likely to have a diagnosis of UTI as those in whom there is suspicion (5.1% versus 5.9%) [46].

The physical examination of children with UTI can be nonspecific. With the advent of ultrasonography, occasionally an anatomically abnormal genitourinary organ may be found during the initial evaluation (eg, hydronephrosis, xanthogranulomatous kidney, protruding ureterocele). An old-fashioned examination, however, still may reveal subtle information suggestive of neurogenic bladder (eg, spinal anomalies, sacral dimples/pits/fat pads).

Diagnosis

The definitive diagnosis of UTI requires a positive urine culture. The urine can be collected in many ways, listed here from the least to most accurate diagnostically: perineally "bagged" urine, clean-catch midstream urine, urethral catheterized urine, and suprapubically aspirated urine [47]. The "bagged" urine technique has a high false-positive rate up to 85% to 99%, and is useful only in ruling out a UTI. Clean-catch technique also may reveal periurethral colonization, complicating the definitive diagnosis. Urinary catheterization yields reliable results but is invasive, and potentially can seed the urinary tract with nosocomial pathogens. The criterion standard is suprapubic aspiration, which yields reliable results and avoids introducing nosocomial pathogens into the urinary tract. If performed under local anesthesia, the procedure is essentially painless. A 21- to 22-gauge needle is used to aspirate the bladder 1 cm to 2 cm above the pubic symphysis. Unfortunately, the variable success rates for obtaining urine (23%–99%) limit its use as a universal way to acquire a urine specimen. The AAP recommends using either catheterized or suprapubically aspirated urine to establish the diagnosis of UTI [1]. Table 2 lists the culture criteria for diagnosis of urinary infection [48].

Because the definitive urine culture takes at least 24 hours to yield useful information, initial urinalysis usually is performed. Results are immediately available that may provide the basis for empirical treatment. The presence of bacteria under high power field represents approximately 30,000 bacteria per milliliter but does not distinguish pathogens from contaminating bacteria. The positive predictive value can be as high as 84.6% if pyuria (more than 10 white blood cells per high power field) is also present [46]. A negative microscopic examination does not rule out UTI.

Chemical screening of infection/inflammation markers also yields useful information (Table 3). The most commonly used markers in a generic urinalysis are nitrite and leukocyte esterase [1]. Nitrite is a by-product of nitrate reduction from bacterial metabolism (particularly from gram-negative organisms). The test is most useful if first-voided morning specimen is analyzed. It may be falsely negative if the urinary nitrates are not reduced by the bacteria, or if the pathogens are gram-positive streptococci. Leukocyte esterase is produced by activated leukocytes, which may or may not be present in the urine, making it a less-accurate tool in diagnosing UTI. Other laboratory tests may be performed, but mostly for assessing the patient's overall health baseline. Complete blood test and C-reactive protein may aid the diagnosis of infection in a lethargic child. A basic metabolic panel may reveal the electrolyte disarray in a dehydrated child with mild renal compromise.

Diagnostic-imaging tests in the acute setting are seldom essential, except when there are gross genitourinary abnormalities [49]. Most often radiologic studies can be performed when the acute infection subsides because immediate management usually is based on clinical findings. MRI and dimercaptosuccinic acid may document acute renal involvement, however. The goals of radio-

Table 2
Culture criteria for diagnosis of urinary tract infection

Method of collection	Colony count	Probability of infection (%)
Suprapublic aspiration	Gram-negative rods, any number	99
	Gram-positive cocci, more than a few thousand	95
Catheterization	$>10^5$	Infection likely
	10^4–10^5	Suspicious; repeat
	10^3–10^4	Infection unlikely
Clean voided (male)	$>10^4$	Infection likely
Clean voided (female)	three specimens: $>10^4$	95
	two specimens: $>10^5$	90
	one specimen: $>10^5$	80
	5×10^4–10^5	Suspicious; repeat
	10^4–5×10^4	Symptomatic, suspicious; repeat
	10^4–5×10^4	Asymptomatic; infection unlikely
	$<10^4$	Infection unlikely

Data from Hellerstein S. Recurrent urinary infections in children. Pediatr Infect Dis 1982;1:271–81.

Table 3
Sensitivity and specificity of components of urinalysis

Test	Sensitivity (%)	Specificity (%)
Leukocyte esterase	83 (67–94)	78 (64–92)
Nitrite	53 (15–82)	98 (90–100)
Leukocyte esterase and nitrite	93 (90–100)	72 (58–91)
Microscopic white blood cells	73 (32–100)	81 (45–98)
Microscopic bacteria	81 (16–99)	83 (11–100)
Leukocyte esterase, nitrite, or microscopic positive	99.8 (99–100)	70 (60–92)

Data from American Academy of Pediatrics, Committee on Quality improvement, Subcommittee on Urinary Tract Infection. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. Pediatrics 1999;103:843–52.

logic studies are to identify correctable anatomic anomalies predisposing a child to UTI, to examine baseline renal anatomy, and to provide guidance in preserving future renal function.

The most common finding is vesicoureteral reflux (VUR), found in 50% of children younger than 1 year of age with UTI [50]. The grades of VUR correlate with risk for renal damage. Patients with high-grade VUR are four to six times more likely to have renal scarring than those with low-grade VUR, and eight to 10 times more likely than those without VUR [1]. Obstructive lesions can be found in 5% to 10% of children with UTI as well [16]. Although recommendations related to the need and extent of radiologic imaging have been controversial because some investigators believe that abnormal findings may have no measurable public health and rare, individual, long-term consequences, the incidence of UTI-associated genitourinary anomalies is considerable.

Complications

Although rare, UTI may result in severe sequelae with major morbidity and even mortality. Serious sequelae of UTI include pyonephrosis; perirenal, renal, and retroperitoneal abscesses; and other processes, such as emphysematous and xanthogranulomatous pyelonephritis (XGP) and infective calculus.

In this era, abscesses in the perirenal, renal, and retroperitoneal spaces are mostly the result of pyelonephritis rather than seeding from other systemic or skin infections as seen in the preantibiotic era. Improvement in imaging techniques and availability of newer generations of antimicrobial agents have changed the management of these suppurative diseases [51]. These abscesses arise from either hematogenous spread of extragenitourinary infectious sites (usually staphylococcus), or direct extension of ascending urinary infection and pyelonephritis (usually gram-negative organisms). The traditional treatment is a combination of antibiotics and drainage. More recent data, however, have shown that treatment with antimicrobial agents alone may be as effective as surgical drainage in stable patients [52]. Focal pyelonephritis (lobar nephronia), however, may be difficult to differentiate from a renal abscess by imaging techniques alone.

Pyonephrosis is characterized by the presence of purulent materials in the urinary collecting system, the result of infection in an obstructed collecting system. On imaging study, a layered appearance of the debris may be observed. The treatments are prompt drainage of the collecting system and concomitant antibiotics [17,53].

XGP is a rare inflammatory condition resulting from chronic bacterial infection of the kidney and collecting system obstruction. A recent large series [54] reported two etiologies, obstructive and nonobstructive, in 21 cases. The common features are renal mass, hematuria, anemia, and leukocytosis. In the obstructed group, 100% had nephrolithiasis, 69% had isolation of *Proteus mirabilis*, and 54% had recurrent UTI. In comparison, 33% of the nonobstructed group had acute inflammatory syndrome. In the nonobstructed group it is particularly difficult to distinguish XGP from renal tumor. Surgical extirpation is curative.

Calculus of the urinary tract is the result of urinary stasis or urea-splitting uropathogens. UTI contributes to few nephrolithiasis in children [55]. The consequences of stone disease in children are recurrent or persistent UTI, acute pyelonephritis, and obstruction of collecting system and XGP. Because the disease is often sporadic, careful long-term follow-up of the patients with active and inactive stone disease is mandatory.

Emphysematous cystitis and *pyelonephritis* are acute suppurative diseases of the bladder and kidney resulting from UTI from gas-forming pathogens, mostly gram-negative rods and yeasts. Diabetic and other immunosuppressed patients are at higher risk. Emphysematous infections are labile and rapidly progressive, demanding prompt diagnosis and intervention [56].

Consequences of urinary tract infection

Pediatric UTI can cause acute morbidity and result in clinic visits, antimicrobial usage, exposure to radiation, hospitalization, and loss of parental work force associated with their child's care. Long-term consequences are potential renal damage, recurrent infection, and occasional renal function deterioration and hypertension.

Infants and young children are at higher risk than older children for incurring acute renal injury with UTI. The risk for renal damage is additive as the number of recurrences increases [57]. The risk for hypertension predisposes these children to other blood pressure–related morbidities when they reach adulthood. In one study, 12.8% of the children with a history of UTI and surgically corrected VUR developed hypertension over a 10-year follow-up; 17% of the hypertension occurred in children with gross renal scarring [58]. The worst consequence is the loss of renal function and resultant end-stage renal disease requiring dialysis or renal transplantation. Various studies claim that up to 13.6% of patients with reflux nephropathy develop end-stage renal disease [59]. UTI warrants special attention regarding its proper diagnosis, timely management, and effective prevention of reinfection to minimize renal damage and associated sequelae.

Summary

UTI is a common problem in the pediatric population with significant morbidity. *Escherichia coli* is the most common pathogen in pediatric UTI of all ages. The fecal-urinary route is the most common pathway of pathogenic spread, although seeding from systemic infection and nosocomial introduction may occur. The pathogenesis of UTI is appreciated better because of recent advances in understanding of pathogen–host interaction. It is particularly important for clinicians to be vigilant in examining risk factors and diagnosing UTI in young children. A positive urinary culture confirms the diagnosis of UTI if the urine sample is obtained properly. When a child responds appropriately to antimicrobial therapy, acute imaging studies are seldom necessary. In rare cases, however, the consequences of pediatric UTI can be dire, including immediate complications such as pyelonephritis, abscesses, pyonephrosis, infection stones, and xanthogranulomatous pyelonephritis, and more remote complications such as hypertension, renal insufficiency, and end-stage renal disease.

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Urinary tract infections in children: treatment

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Urinary tract infections (UTIs) are among the most common reasons for referral of a pediatric patient to the urologist. Identification of an anatomic or physiologic predisposition to urinary infections is an integral part of the comprehensive management of pediatric UTIs. (Please see the article by Shortliffe appearing elsewhere in this issue for a discussion of the etiology and epidemiology of urinary tract infections in children.) The objectives in treatment of UTIs include eradication of infection, symptomatic relief, and prevention of renal damage. Prevention of renal parenchymal scarring is the most important goal, and is possible with early, aggressive treatment of acute pyelonephritic episodes in children, as well as prompt management of acute and recurrent lower UTIs. This article outlines the therapeutic options for treatment of upper and lower UTIs of various etiologies in children.

Lower urinary tract infections

Acute bacterial cystitis

Multiple options are available to the practitioner to treat uncomplicated lower UTIs. These options include sulfonamides, trimethoprim/sulfamethoxazole (TMP/SFX), nitrofurantoin, cephalosporins, and trimethoprim alone. Fluoroquinolones are effective against various microbes, including most gram-positive and -negative organisms. Fluoroquinolones provide excellent coverage against *Pseudomonas aeruginosa* and *Proteus* species. Previously, concerns regarding arthrotoxic effects, including cartilage toxicity, had discouraged the use of quinolones in children. Clinical evidence has not supported these concerns, however, and multiple trials [1,2] examining ciprofloxacin in children initially have shown it to be safe in children with cystic fibrosis.

One of the largest studies [1] involved 1795 patients receiving intravenous or oral ciprofloxacin courses. Treatment-associated events were reported in 11% of children receiving oral ciprofloxacin compared with 19% among intravenous recipients. Overall arthralgia occurred during 1.5% of treatment courses. Most events were of mild to moderate severity and self-resolving. This adverse event pattern was similar to that observed in adults. A multicenter clinical trial is underway to evaluate the use of ciprofloxacin in children with complicated UTIs. Data from this study also will address the safety profile of ciprofloxacin when used to treat UTIs.

Before selecting from the antibiotic arsenal, the practitioner considers the susceptibility pattern of the offending organism, and determines whether adding an intramuscular dose of antibiotic to an oral course of therapy is beneficial. A study that investigated 287 children with febrile UTIs over multiple years showed that the susceptibility pattern of *Escherichia coli* (the most frequently isolated organism) to nitrofurantoin and nalidixic acid remained excellent over time, but resistance to TMP/SFX was significantly higher [3]. Baker and colleagues [4] performed a prospective randomized trial in which 69 children 6 months to 12 years of age with febrile UTIs received either a dose of intramuscular ceftriaxone in addition to a 10-day course of TMP/SFX or oral therapy alone. They found no difference at 48 hours in the urine sterilization rate, clinical improvement, or

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subsequent hospital admission rate of the patients. Oral cefixime (8 mg/kg/d) also has been explored as a first-line therapy with encouraging results and efficacy comparable to intravenous cefotaxime or oral TMP/SFX [5,6].

The optimal duration of treatment in pediatric, uncomplicated, acute lower UTIs is controversial. Multiple studies have examined the relative merits of short-course (one dose or up to 4 days) versus longer-course (1–2 weeks) antibiotic treatment. In multiple studies [7–11] results were better with long duration, with an attributable improvement in outcome of 5% to 21%. A recent review and statistical analysis by Michael and colleagues [12], however, was published examining 10 trials covering 652 patients 3 months to 18 years of age. There was no significant difference in the frequency of positive cultures between the short- (2–4 days) and longer-duration (7–14 days) antibiotic therapy at either 0 to 10 days after treatment or 1 to 15 months after treatment. Furthermore, there was no significant difference in the development of resistant organisms after therapy. Another study conducted by Helin [13] prospectively examined a 3-day course of TMP/SFX versus a 10-day course and surprisingly found a higher rate of recurrence over 11 months in the 10-day therapy cohort. Based on available data and current practice, a short-course of antibiotic therapy consisting of 3 days of treatment in a clinically stable older child is probably sufficient [12]. In children 2 months to 2 years of age, the longer course of treatment should be considered strongly.

If an infant is 3 months of age or younger, or a young child with a suspected UTI is dehydrated, toxic, or unable to retain oral intake, initial antimicrobial therapy should be administered parenterally and hospitalization should be advised [14]. Nelson, Gurr, and Schunk [15] demonstrated that children presenting with a UTI and a temperature greater than 40°C had a higher rate of outpatient-treatment failure and warrant consideration for hospitalization.

Eradication of the infection should be documented with repeat urine cultures. After urinary sterilization in children, prophylactic doses of antibiotics are recommended as clinically indicated until further work-up with imaging studies is completed [14].

Treatment of underlying voiding dysfunction and constipation is essential to successfully managing pediatric UTIs. Radiologic studies have documented an association between fecal loading seen on abdominal radiographs and recurrent UTIs [16]. Additionally, breastfeeding offers significant protection against UTIs in infants [17]. Human breast milk contains several factors with anti-infectious potential, including immunoglobulins (especially secretory IgA), oligosaccharides and glycoproteins with antiadhesive capacity, and cytokines. Some of the protective effects may derive from an altered mucosal colonization pattern in the breast-fed infant.

Viral cystitis

Viral infections of the bladder, although irritative and at times impressive in their scope, are self-limited. Supportive care with anti-inflammatory medications and adequate hydration are often all that are required. Ultrasound imaging may reveal global or focal thickening of the bladder wall (Fig. 1). In immunocompromised patients with acute adenovirus hemmorhagic cystitis, the use of ribavirin has been suggested [18].

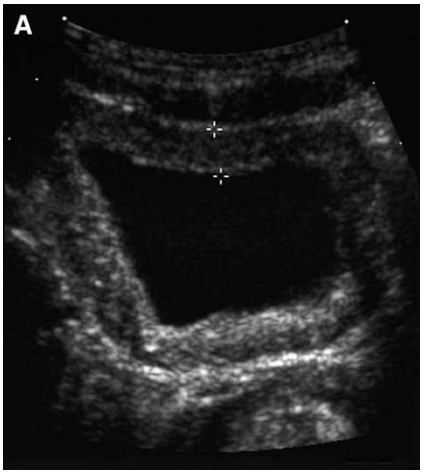
Schistosomiasis

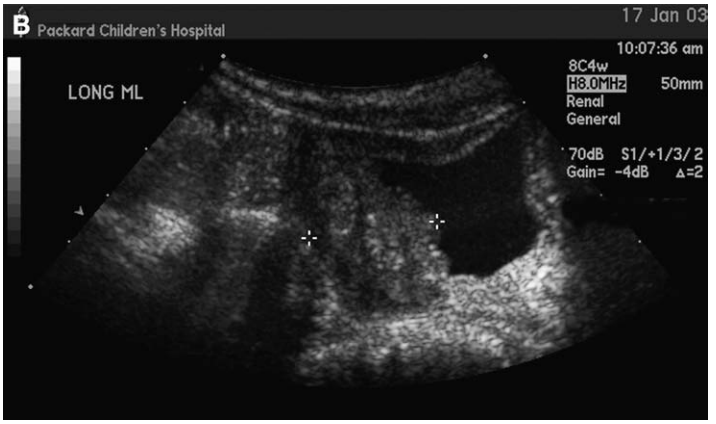
Various treatments are available for the treatment of schistosomiasis, a parasitic infection. Unfortunately, most of the available medications carry significant side effects. The current drug of choice is praziquantel, which, unlike some other medications used to treat schistisomal infections, is effective against all species of the organism. It is administered orally as a single or divided dose of 40 to 60 mg/kg/d [19]. Surgical intervention in schistosomiasis should be reserved until the results of medication and conservative management can be assessed.

Long-term infection may lead to significant fibrosis and bladder contracture. Augmentation cystoplasty, autoaugmentation, or bladder replacement may be needed. Bilharzial infection also can lead to distal ureteral strictures and subsequent obstructive uropathy. Unfortunately, the concomitant fibrosis of the ureteral and bladder walls usually precludes ureteroneocystotomy by way of submucosal tunneling as an option. Partial-flap ureteroneocystotomy has been described [20] to alleviate such distal obstruction.

Enterobiasis

Pinworm infestation, although a disease of the gastrointestinal tract, has been implicated as a factor in acute and chronic UTIs. Medical therapy is indicated for affected individuals. One dose of pyrantel pamoate (11 mg/kg, with a maximum of 1 g), repeated in 2 weeks' time, is the





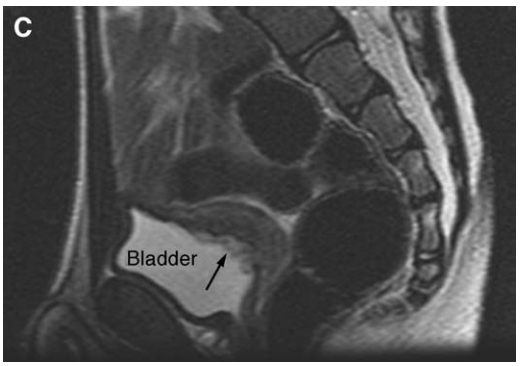


Fig. 1. (*A*) Ultrasonograph of the bladder in child with adenovirus cystitis. Crosshatches reflect global thickening of bladder wall. (*B*) Pretreatment ultrasonograph of the bladder in 5-year-old boy with adenovirus cystitis. Crosshatches reflect focal thickening of bladder wall at the dome. (*C*) Pretreatment MRI of the bladder in 5-year-old boy with adenovirus cystitis. Arrow demonstrates focal thickening of bladder wall at the dome. (*D*) Posttreatment ultrasonograph of the bladder in 5-year-old boy with previous adenovirus cystitis. Arrow demonstrates resolution of focal thickening of bladder wall at the dome.

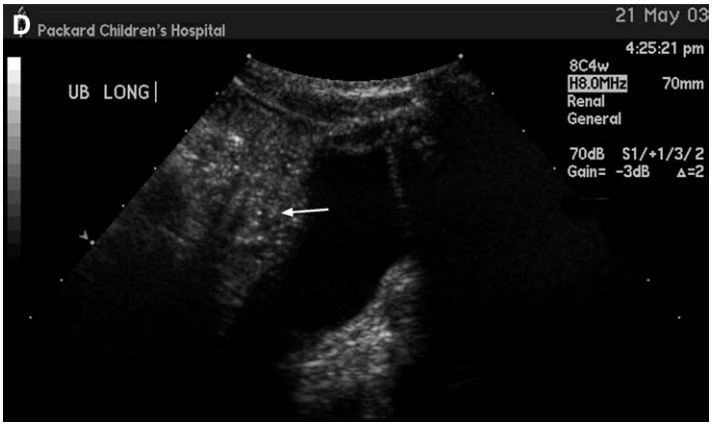


Fig. 1 (*continued*)

treatment of choice. Mebendazole, 100 mg, with a repeat dose at 2 weeks is an alternative treatment. Neither drug is approved by the US Food and Drug Administration in children under 2 years of age.

Chlamydia

Chlamydial infections in children generally fall into two categories: perinatally transmitted cases, and sexually transmitted cases in older children. In younger children the physician must be vigilant for evidence of sexual abuse; if suspected, appropriate hospital and social service guidelines should be followed. Possible treatment agents include sulfonamides, erythromycin, and tetracyclines, usually given for a 10- to 14-day course. Tetracyclines should not be administered to children under 8 years of age because they can stain permanent teeth [21].

Epididymitis

The treatment of acute epididymitis includes scrotal elevation and support, and analgesic/anti-inflammatory medications. If a bacterial source is suspected, an antibiotic can be started after obtaining a urine culture. For gonococcal epididymitis, intramuscular ceftriaxone can be administered. Chlamydial infections can be treated with sulfonamides, tetracyclines (in patients older than 8 years of age), and erythromycin. Enteric bacterial infections should be treated with broad-spectrum antibiotics. Once the infection is treated, age-appropriate studies should be performed to determine the etiology of the epididymitis. There seem to be distinct causal agents of epididymitis; in the infant group, an anatomic anomaly is more likely to be the cause. Work-up may include ultrasound, voiding cystourethrogram, or CT scan.

In early pubertal boys functional voiding problems can play a leading role. Dysfunctional voiding and postponement of urination theoretically can produce high pressures in the prostatic urethra as well as the bladder. The patency of the ejaculatory duct valves may be overcome by attempts to maintain continence and allow for urethrovasal reflux and a "chemical" epididymitis [22]. Behavior modification with timed voiding and relaxation during voiding may be needed in such cases. Further evaluation in the office can include renal/bladder ultrasound and a uroflow study with post-void residual check (Fig. 2).

Upper urinary tract infections

Pyelonephritis

Treating a child with suspected pyelonephritis rapidly and successfully is of utmost importance because the timeliness of effective therapy can influence the amount of renal scarring and loss of function. Conventional thinking had placed infants and children under 5 years of age in the highest risk category for renal scarring and sequelae. Studies have shown, however, that there is no evidence of attenuated risk with older children and all patients must be treated and monitored carefully [23].

There is considerable ambiguity and controversy regarding which patients require hospitalization and parenteral antibiotics, and which may be treated effectively as outpatients. Older children who tolerate oral intake and who do not

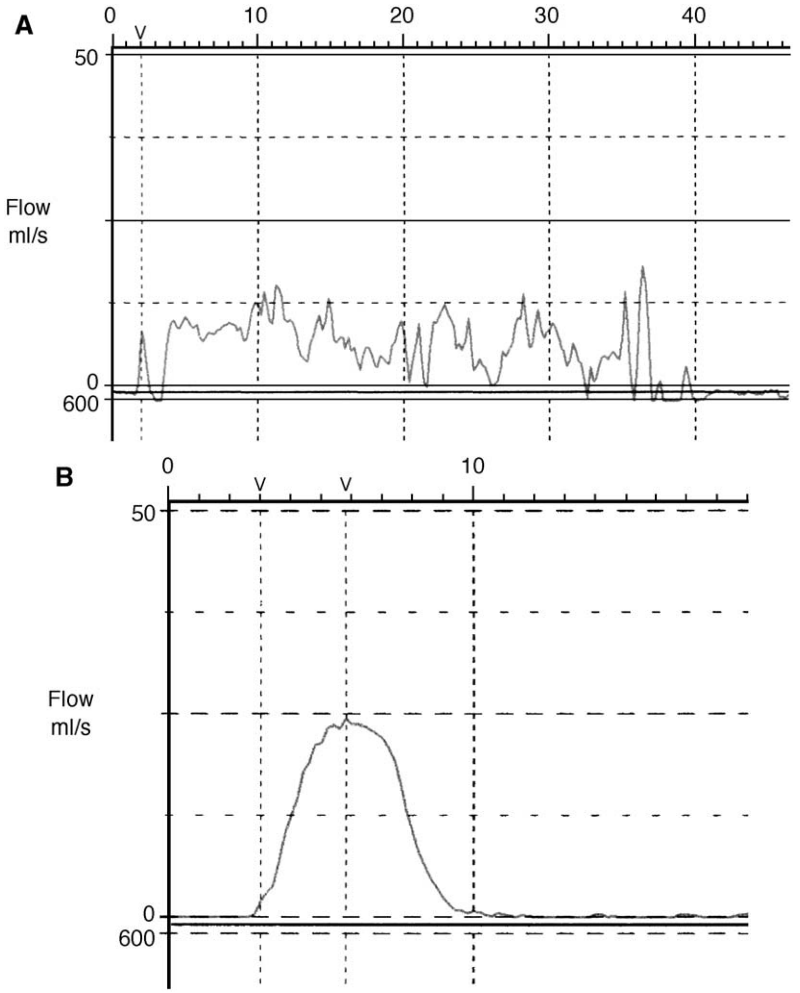


Fig. 2. (*A*) Office uroflow study from a 9-year-old boy presenting with epididymal inflammation. Tracing demonstrates the staccato flow pattern and prolonged voiding interval of a child with dysfunctional voiding. (*B*) Office uroflow study from same boy after appropriate interventions to treat dysfunctional voiding. Tracing demonstrates the laminar flow pattern of a child with healthy voiding hygiene.

appear septic can be treated with oral therapy. Options include TMP/SFX, nitrofurantoin, or cephalosporins. Alternatively, patients with clinical pyelonephritis can receive an intramuscular injection of a third-generation cephalosporin (eg, ceftriaxone) until culture-specific oral agents are identified. This injection should be followed by 10 to 14 days of appropriate oral therapy. Antibiotic sensitivities need to be followed on culture and may require a change in agent.

If a child appears clinically toxic or septic, however, initiation of therapy with hospitalization and parenteral therapy will be necessary. In addition, neonates warrant strong consideration for treatment as inpatients. In these patients, rehydration and initiation of broad-spectrum antibiotics (traditionally ampicillin and gentamicin) is appropriate until culture results and sensitivities are available. Alternatively, a third-generation cephalosporin may be used, but this will not cover enterococci. In neonates, intravenous antibiotics should be continued for 7 to 10 days. Culture-specific treatment doses of oral therapy should continue to complete 14 days of treatment. In patients older than 2 months of age, once they have been afebrile for 24 to 48 hours and serum markers of infection (ie, elevated white blood cell count or C-reactive protein) have normalized,

substitution of oral medication to complete a long (10–14 day) course of total therapy is reasonable. Follow-up urine cultures are important to document eradication of infection. Prophylaxis should be administered until evaluation of the urinary tract is completed.

Renal abscess

Appropriate antibiotic therapy is the first step in guiding treatment. Classically, this therapy has been combined with surgical drainage to address the infection properly. More recently, percutaneous CT– or ultrasound-guided drainage can be used to obtain a culture and drain the collection. Drainage can be a solitary aspiration or continual drainage with the placement of a percutaneous pigtail catheter. Follow-up imaging is necessary to confirm resolution. Many cases can be managed without surgical intervention. If the abscess fails to resolve with a conservative approach, surgical drainage is the definitive treatment. *Focal bacterial nephritis* (*acute lobar nephronia*) is a focal form of acute bacterial nephritis, affecting one or more renal lobules. The most common causative organism is *E coli*, although infections also occur with *Staphylococcus aureus, Pseudomonas aureginosa, Klebsiella* species, and other organisms. Ultrasound is a helpful screening tool for hyperechoic or hypoechoic lesions, and CT is accurate in diagnosis (Fig. 3). Timely diagnosis and treatment is crucial because a significant percentage of these patients can progress to renal abscess. Klar and colleagues [24] treated 16 patients diagnosed with acute lobar nephronia, 25% of which evolved to renal abcess. Antibiotic treatment should last for 4 weeks, with resolution of abscess confirmed radiographically. If a staphylococcus infection is suspected because of hematogenous spread, the antibiotic of choice is penicillinase-resistant penicillin. If a patient is penicillin-allergic, treatment with vancomycin or cephalosporin is indicated.

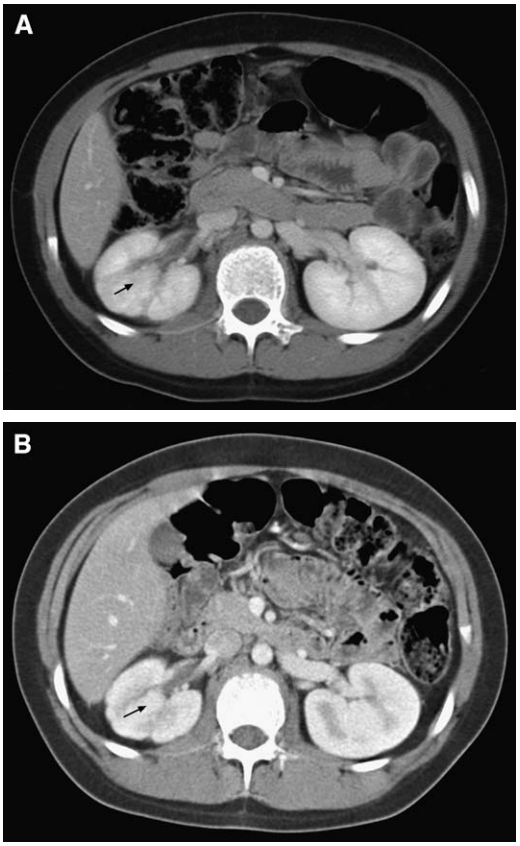


Fig. 3. (*A*) Pretreatment contrast-enhanced CT scan of an 8-year-old girl with right vesicoureteral reflux presenting with pyelonephritis. Arrow demonstrates focal bacterial nephritis (lobar nephronia) affecting middle lobule. (*B*) Posttreatment contrast-enhanced CT scan of the same girl with focal bacterial nephritis. Arrow demonstrates resolution at middle lobule with uniform contrast enhancement in right renal unit.

Tuberculosis

According to recommendations of the American Academy of Pediatrics [25], treatment of genitourinary tuberculosis consists of 9 months of isoniazid and rifampin. For the first 2 months of therapy, a third medication should be added, such as streptomycin, pyrazinamide, ethambutol, or others. Ethambutol should not be used in young children because it has the possible side effect of optic neuritis, and such children may not be able to cooperate with a detailed eye examination. In children with HIV, treatment with three drugs must continue throughout therapy and may need to continue beyond 9 months.

The need for surgical intervention in children with tuberculosis usually is limited to long-term complications in a small percentage of patients. These complications include repair of ureteral strictures, ureterovesical-junction reconstruction in newly incompetent ureteral orifices, or augmentation cystoplasty in small, contracted bladders.

Xanthogranulomatous pyelonephritis

A condition of obscure etiology, *xanthogranulomatous pyelonephritis (XGP)* most often affects middle-aged or elderly women, but is seen

occasionally in children. The most common organisms isolated include *Proteus mirabilis* and *E coli*. Severe in nature, XGP can lead to widespread renal damage. Often the affected renal unit is nonfunctional. Frequently XGP is seen in association with staghorn calculi of the kidney. Nephrectomy usually is required, but partial nephrectomies have been done in focal cases (Fig. 4). Associations between XGP and renal-cell carcinoma, papillary transitional-cell carcinoma, and squamous-cell carcinoma of the renal pelvis have been documented in adults and support performing total nephrectomy in patients [26].

Candidiasis

The treatment of candiduria depends on the extent of infection. In otherwise healthy children who develop candiduria after protracted courses of broad-spectrum antibiotics, discontinuation of the therapy should lead to spontaneous clearance of the fungal infection. Symptomatic infections limited to the bladder may be eradicated by instillation and irrigation of the bladder with a solution of amphotericin B (5% in sterile water, shielded from light). Alternatively, a patient can be treated with urinary alkalization.

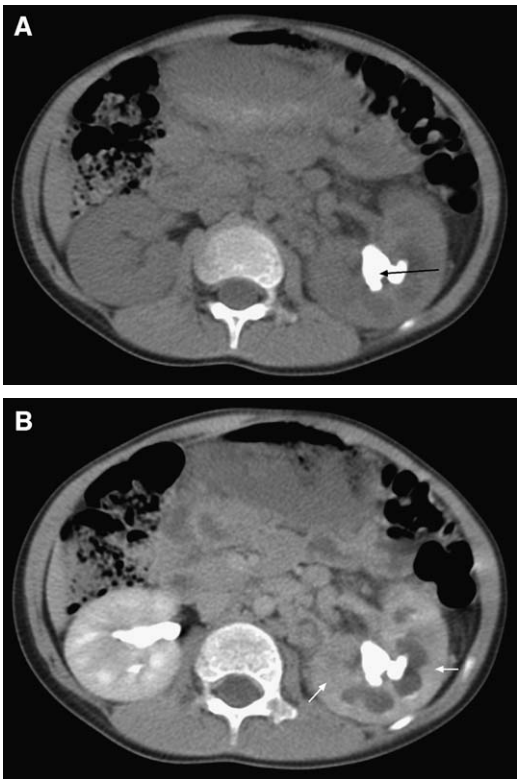


Fig. 4. (*A*) Non–contrast-enhanced CT scan of a 4-year-old girl with XGP in left kidney. Arrow demonstrates staghorn calculus in collecting system. (*B*) Contrast-enhanced CT scan of same girl with XGP in left kidney. Arrows demonstrate nonfunctioning renal parenchyma. Complete nephrectomy was performed after period of nephrostomy tube drainage reveal no return of renal function. (Courtesy of J. Abidari, MD, Stanford, CA.)

Upper-tract candidal infections also can be treated by irrigation with amphotericin B through an existent nephrostomy tube. Alternatively, oral 5-flucytosine may be given, but is contraindicated in children with renal azotemia or bone-marrow depression. Obstructing fungal balls in the renal pelvis may require percutaneous or surgical removal by way of pyelotomy, followed by nephrostomy-tube irrigations. Infected tubes need to be replaced and exchanged for new ones. Forced diuresis with furosemide to clear fungal balls from the renal pelvis without the use of nephrostomy tubes has been reported [27].

The nephrotoxicity of amphotericin B is well documented, and monitoring of renal function is necessary. Medications for the treatment of candiduria include ketoconazole and fluconazole (initial dose 10 mg/kg; maintenance 5 mg/kg for 1–2 weeks), with less associated nephrotoxicity.

Aspergillosis

After *Candida* species, *Aspergillosis* species is the second most common fungal infection in immunocompromised patients. Treatment is similar to that of candiduria, with high-dose intravenous amphotericin B as first-line therapy. As with candiduria, with fungal balls in the renal pelvis, percutaneous or open surgical removal is occasionally necessary, followed by upper-tract irrigation with amphotericin through a nephrostomy tube.

Echinococcosis (hydatid cyst disease)

The most common location for hydatid cyst disease in humans is in the kidneys (approximately 3% of all infections). Albendazole (15 mg/kg/d divided into three doses for 28 days) is the preferred drug for medical management, and must be taken for 4 weeks at a time. As many as four courses can be taken with 15-day intervals between courses. Positive responses are seen in 40% to 60% of pediatric patients treated. Percutaneous management of the disease through cyst drainage with ultrasound guidance has become more successful

in resolving the disease. There is a risk for systemic anaphylaxis reaction with the spillage of cyst fluid. Surgical intervention is also an option for solitary lesions or failed medical management. Care must be taken to avoid spillage during resection because this can seed the abdomen or lead to anaphylaxis.

Summary

Timely treatment of UTIs is imperative in improving the health of children and preventing long-term sequelae. Failure to do so may lead to disseminated infections, renal scarring and hypertension, renal insufficiency, or other serious complications. A vigilant and aggressive practitioner should be able to prevent these adverse sequelae through thoughtful and appropriate therapy. Identification of an anatomic (ie, vesicoureteral reflux) or a physiologic (ie, dysfunctional voiding) predisposition to UTIs is a part of the comprehensive management of pediatric UTIs.

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Vesicoureteral reflux: who benefits from surgery?

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Over the last quarter century, urologists have enjoyed increasing familiarity with open antireflux operations. Success rates of the open antireflux techniques exceed 95% with rare complications. The length of stay and postoperative care have improved to the point that many children leave the hospital without a catheter on the first postoperative day. The development of minimally invasive endoscopic and laparoscopic techniques promises to further reduce operative morbidity. Because of the high success, low complication, and quick recovery rates, the popularity of contemporary antireflux operations now surpasses that of the once common Y-V bladder neck plasty and the female meatotomy used to treat reflux [1,2].

In many ways, reflux has become the "prostate cancer" of pediatric urology. Increased recognition of the association between urinary tract infections and reflux, sibling screening, and evaluation of antenatal hydronephrosis have resulted in an increase in the diagnosis of reflux early in life. Similar to men with prostate cancer, many children with reflux left untreated would sustain no untoward affects of their condition; however, the disease can be severe and even life threatening. Antireflux operations, like radical prostatectomy, have been refined and improved, but it remains difficult to determine which individuals will truly benefit from these operations. To assist the urologic oncologist with these decisions, multivariate nomograms and prospective trials assessing these variables have been developed. Similar nomograms could and should be developed to assist the urologist in the decision to perform an antireflux operation.

In analyzing the outcome of reflux treatment, pediatric urologists have a distinct advantage over surgeons treating prostate cancer. Because the diagnosis of reflux occurs at a young age, the incidence of significant comorbidities is minimal, which facilitates long-term follow-up with respect to disease-specific morbidity. Such follow-up is necessary, because 30 to 40 years may pass between the first renal-scaring pyelonephritis and the development of hypertension or end-stage renal disease [3].

Recognition of the need for such follow-up and of the need to determine who benefits from antireflux operations is not new. In fact, in 1966 at a National Academy of Sciences National Research Council meeting on ureteral reflux, a suggestion was made that the most important item to come out of the meeting would be the development of a prospective randomized controlled protocol with long-term follow-up to determine the indications for antireflux operations [4]. Despite this suggestion and several international prospective trials, the question remains unanswered, in large part, because of a paucity of long-term follow-up data from which to construct outcome nomograms relative to prognostic variables.

Who is likely to benefit

Because any child with reflux faces the possibility of experiencing pyelonephritis and renal damage, a better question asks, "Who is likely to benefit from an antireflux operation?" To determine the answer to this question, the benefits of the operation must be weighed against the risks

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and benefits of doing nothing, or of placing the child on antibiotic prophylaxis and obtaining follow-up cystograms. Children with a positive outcome from surgical intervention include those in whom renal damage and its sequelae were prevented but would have occurred if these children had been treated with antibiotics or had no treatment. Other children who benefit include those who would have sustained significant side effects of antibiotic prophylaxis or catheterization and cystograms. Intuitively, the risks of side effects from antibiotics and catheterization increase with the duration of reflux and nonoperative treatment.

If antireflux operations were without the risk of complications, all children with reflux would undergo the operation, because all children with reflux have some degree of risk for renal injury, and all antibiotics have potential side effects. Unfortunately, no operation is without risk. Complications of any antireflux operation include infection, injury to the bladder, obstruction of the ureter, failure of resolution, and anesthetic reactions. Furthermore, the effectiveness of antireflux operations for preventing renal damage remains unclear. To answer the question of who is likely to benefit from an antireflux operation, multiple factors must be considered:

- Who is at greatest risk for renal damage that can be prevented by an antireflux operation?
- Who cannot sustain further renal damage without significant impairment to their health?
- Who is unlikely to resolve reflux?
- Who is likely to have a complication from atireflux surgery?
- Who is at risk for side effects of antibiotics and cystograms or doing nothing?

Treatment versus no treatment

Several large prospective studies have attempted to address the question of operative intervention versus antibiotic prophylaxis in children with reflux [5–9]. The outcomes of these studies have generally shown no significant difference in renal function or growth, the progression or development of new scars, or urinary tract infections. Pyelonephritic symptoms tend to be more common in the medically treated groups compared with the surgical groups [10–12]. The likelihood of new scars occurs early in children treated surgically when compared with those in the medical groups [13]. This observation suggests a potential benefit from the antireflux operations for some patients; however, other researchers have suggested that, once renal scarring has occurred, the disease tends to run its course, and operative treatment has little benefit [3,14]. If this is true, treatment should be aimed at early diagnosis and prevention with antibiotic prophylaxis or prompt treatment of pyelonephritis [3].

Others question the need for antibiotic prophylaxis, suggesting that, in select individuals, the chance for pyelonephritis and renal damage off prophylactic antibiotics is small [10,15–17]. Because the diagnosis of reflux often follows a urinary tract infection, it leads many individuals to the erroneous assumption that reflux is responsible for the infection. Unless reflux is massive enough to induce stasis, it does not predispose to urinary tract infections [7,17]. More often, the infections are the result of predisposing conditions such as a previous history of urinary tract infections, female gender, constipation, infrequent voiding, incomplete emptying, and impaired host defenses.

Although it is generally safe and well tolerated, daily antibiotic prophylaxis incurs cost and potential risks to children. Antibiotic prophylaxis for urinary tract infections has also been associated with a 24-fold increased risk of resistant *Escherichia coli* to trimethoprim-sulfamethoxazole [18]. The efficacy of antibiotic prophylaxis for the prevention of urinary tract infections has also been questioned [19]. Some contend that antibiotic prophylaxis is effective and safe for preventing urinary tract infections [20]. No prospective randomized controlled trials have been conducted to evaluate the efficacy of stopping prophylactic antibiotics in a child with reflux, although some researchers have suggested that such a study would be "ethically feasible and scientifically necessary" [17].

Outcome variables

The debate of treatment versus no treatment must be individualized based on an assessment of the child's risk for an adverse outcome from vesicoureteral reflux. Adverse effects of untreated reflux include an increased risk for pyelonephritis. Pyelonephritis may lead to renal damage as evidenced by renal scars. Renal damage may cause hypertension as well as renal insufficiency

or failure [7]. Multiple factors affect the likelihood of developing adverse outcomes and influence the surgeon's decision to operate. For example, should a child with grade 3 reflux be observed, placed on antibiotics, or undergo surgical correction? Any of these answers may be correct depending on the patient's age, gender, history of infections, unilaterality or bilaterality (or solitary kidney), scars, and cause of reflux (primary or secondary).

Age

The risk of renal scars seems to be greatest in younger children (less than 6 years of age) and is highest in the first year of life [3,6,8,17]. A child with an onset of pyelonephritis before age 3 years sustains a greater reduction in the glomerular filtration rate than after age 3 years; however, renal scars may occur in older children if they have recurrent pyelonephritis [21]. This observation suggests an increased susceptibility to infection in the developing kidney. Such susceptibility argues in favor of aggressive prevention of pyelonephritis in the young child.

Most newborns with reflux detected prenatally are boys, and most of these patients have bilateral, high-grade reflux. There is a much higher spontaneous resolution rate associated with this degree of reflux in infants than with a similar grade detected later in life. Apparent scars or regions of focal dysplasia occur in 30% to 50% of infants with dilating reflux [22,23]. Infants diagnosed with high-grade asymptomatic reflux owing to antenatal hydronephrosis or sibling screening seem to have a lower risk of subsequent renal scaring than do infants presenting with infection [24–26]. This observation may reflect a selection bias or a true benefit of antibiotic prophylaxis. Breakthrough infection rates in this population in some series approach 50%, and prophylactic circumcision has been recommended for male infants with reflux [22,25].

For a given grade of reflux, the younger the child is at the time of diagnosis, the higher the chance for spontaneous resolution. For example, a child with bilateral grade 3 reflux diagnosed at 6 years of age or older has a resolution rate of 10% at 5 years compared with a rate of 60% if the reflux is diagnosed at less than 1 year of age [9]. This difference is thought to be related to a change in configuration of the ureterovesical junction with growth, as well as improved voiding dynamics with maturity [27]. If linear growth is responsible for the resolution in reflux, it would seem logical that children in the upper percentiles of the growth curve would have a more rapid resolution of any given grade of reflux relative to smaller stature children. Data relating the resolution of reflux to actual change in height and weight are lacking.

Gender

With the exception of neonates, girls have more urinary tract infections than do boys [17]. Such infections occur in 8% of girls and 2% of boys by 7 years of age, and 10% to 30% of these children sustain at least one recurrence [19]. Breakthrough urinary tract infections are significantly more common in girls than in boys, regardless of vesicoureteral reflux grade [28]. This observation suggests that girls with reflux are at increased risk for infections and scarring, and, indeed, girls have been noted to have a higher rate of new renal scar formation by nuclear renal scans [17]. Boys may also have better resolution rates for low-grade reflux than do girls [29].

Grade of reflux

Increased grades of reflux are associated with decreased resolution rates [9,29]. Children with reflux and urinary tract infections are at increased risk for renal scarring when compared with children with urinary tract infections and no reflux. Multiple studies demonstrate a direct correlation between the increased prevalence of scars and increased grades of reflux [30]. Renal scarring develops less often in nondilating forms of reflux [23,25,31]. In the International Reflux Study, 50% of children with grade 3 or 4 reflux had scars at entry [6]. The risk for renal parenchymal loss has also been shown to be higher in children with grade 3 or greater reflux when compared with children with grade 2 or less reflux [6,21]. Aside from grade, the presence of intrarenal reflux has also been suggested to increase the risk of renal scars, and, experimentally, scars have been demonstrated only at the site of refluxing papillae [14].

Laterality

Bilateral reflux has been associated with decreased resolution rates [9,29]. Bilateral reflux also increases the risk of pyelonephritis and scar formation in both kidneys, which increases the risk of long-term adverse outcomes relative to the risk in a patient with unilateral reflux and a normal contralateral kidney. A patient with reflux into

a solitary functioning kidney is also at increased risk for significant adverse outcomes (ie, renal insufficiency/failure) when compared with a patient with a normal contralateral kidney.

Urodynamics

Reflux occurring secondary to bladder outlet obstruction, such as that associated with posterior urethral valves or neurologic impairment, is well recognized. Spontaneous resolution of reflux in these situations is unlikely without treatment of the primary problem (ie, the obstruction). Complication rates are also significantly higher following antireflux operations for secondary reflux. There is increasing recognition that many children with reflux, perhaps over 40%, have associated voiding dysfunction or dysfunctional elimination creating a functional obstruction [32]. By treating the primary problem, multiple studies have demonstrated a direct correlation between successful treatment of constipation, dysfunctional voiding, and uninhibited bladder contractions and improved rates of urinary tract infections and reflux resolution [32–35]. Voiding dysfunction is also a significant risk factor for the development of new scars [27]. A careful history assessing bowel and bladder habits should be obtained in children with reflux, because the treatment of bowel and bladder abnormalities significantly improves reflux resolution when compared with the outcome in children with similar grades of reflux and no bowel or bladder dysfunction [36,37].

Because of the prevalence and significant impact of bladder dysfunction on reflux, a rationale exists for performing formal urodynamic studies in children with reflux [27,37]. Unfortunately, formal fluoroscopic-urodynamic studies are invasive and result in increased radiation exposure relative to nuclear cystograms. Several investigators have looked at the relationship between intravesical pressure and vesicoureteral reflux [37]. Because bladder pressure overcoming the pressure in the ureter and ureterovesical junction drives reflux, an incompetent or patulous ureterovesical junction would intuitively reflux urine at a low bladder pressure. This situation may result in a higher grade of reflux, assuming a larger volume of urine is refluxed. Nevertheless, multiple variables could affect the amount of urine refluxed, and a more direct measurement of the ureterovesical junction competence may be the bladder pressure at which reflux first occurs. Because the ureterovesical junction is not static but changes configuration with bladder filling, the pressure at the onset of reflux and the bladder volume at the onset of reflux could potentially provide prognostic characteristics of the ureterovesical junction. A nuclear cystometrogram performed with a 6F dual-lumen urodynamic catheter permits simultaneous monitoring of bladder pressure and volume [38]. This technique is no more invasive than a standard nuclear cystogram. Preliminary data obtained with this technique suggest that a combined reflux pressure/bladder volume index is more predictive of reflux resolution than is grade alone [38]. It remains to be determined whether reflux pressure with this technique will be a prognostic factor independent of bladder volume at the onset of reflux.

Scars

One third of patients with reflux have renal scars [11,39]. The presence of scars implies regions of renal damage and increases the risk for long-term adverse sequelae. In the newborn with reflux, scars have been detected before the occurrence of infection. These "scars" are thought to be regions of focal dysplasia resulting from abnormal nephrogenesis as opposed to damaged normal tissue following pyelonephritis. It is possible that a region of focal dysplasia does not contain the same mechanisms of creating hypertension as that found in a focal renal pyelonephritic scar. Although the ultimate significance of these regions of dysplasia remains to be determined through careful long-term follow-up, it is clear that these regions of diminished renal function can be associated with significant morbidity and mortality [23].

Children with renal scars are more likely to have additional scars than are children without renal scars [25,40,41]. In one study with a mean follow-up of 12 years after an antireflux operation, children with unilateral renal scars had an 11% chance of sustaining hypertension and an 18.5% chance if they had bilateral renal scars [42]. Another study also suggests that the incidence of hypertension in children with bilateral renal scars is about 20% [43]. Children with severe bilateral renal scars are significantly more likely to sustain proteinuria, chronic renal insufficiency, and renal failure than are children with unilateral scars or unscarred kidneys [44,45]. This high-risk group requires prevention of further damage from pyelonephritis.

Urinary tract infections

As mentioned previously, many factors aside from high-volume reflux predispose a child to urinary tract infections, including a previous history of such infections, female gender, constipation, infrequent voiding, incomplete emptying, and impaired host defenses [46]. Most of these factors have been noted previously as risk factors for an adverse outcome from reflux. A child with impaired host defenses at a cellular receptor or immunologic level may most easily be assessed by his or her history of urinary tract infections.

A child diagnosed with asymptomatic reflux based on screening is at a lower risk for urinary tract infections and renal scars than is the child with a history of reflux presenting after an infection [25]. Girls with a history of childhood urinary tract infections and reflux have a significantly increased risk for urinary tract infections during adulthood, with an incidence of about 40% [45]. These girls have an increased risk during pregnancy regardless of the presence or absence of reflux, although the incidence seems to decrease in those with resolution of reflux [13,45]. Children with breakthrough urinary tract infections may also be less likely to have reflux resolution when compared with children with no further infections [43].

Prompt treatment of pyelonephritis reduces the risk of renal damage [47–49]. The parent and primary care physician's likelihood of compliance with a policy of maintaining a high index of suspicion and initiating prompt treatment of urinary tract infections must be factored into the urologist's decision analysis regarding management of the child with reflux. This factor is critically important in the young child with high-grade reflux.

Summary

Continued improvement in minimally invasive antireflux operative techniques, as well as improved cystogram techniques [50], may affect decisions regarding reflux management. An informed decision must weigh the risks and benefits of the alternative methods of management. To this end, urologists must strive to collect better prospective and retrospective data regarding outcome in children with reflux.

The answer to the question of who will benefit from an antireflux operation remains unknown. To truly answer the question, a large prospective randomized placebo-antibiotic-operation study with long-term follow-up would be needed. Such a study will not happen for all groups of children with reflux, although it may occur for particular subgroups of refluxing children. Currently, the decision to operate on a child with reflux or to continue or stop antibiotic prophylaxis is based on the physician and parent's assessment of the risks and benefits. Factored into this analysis is the likelihood for resolution. Multiple variables affect the child's risk of long-term adverse outcome and the time to resolution. Currently, treating physicians incorporate what is known about each of these factors for a given child when counseling parents regarding their overall assessment of risk for that particular child.

The future development of nomograms to assess an individual's risk of adverse outcomes should facilitate counseling regarding management options. Factors in this analysis should include age, gender, the history of urinary tract infections, renal scars, bladder and bowel function, as well as reflux grade. Nomograms assessing the probable time to reflux resolution may be improved by incorporating factors in addition to reflux grade. Such factors may involve age, gender, stature, bladder volume and pressure at the onset of reflux, and bladder and bowel function. Improved predictability of the time to resolution of the reflux should assist in treatment decisions and optimize the time for follow-up studies [29,38].

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Vesicoureteral reflux: surgical approaches

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The treatment of vesicoureteral reflux (VUR) has evolved over the past half-century from primarily surgical to nonoperative treatments in most cases [1,2]. Although the benefits of surgical correction versus medical management are debated, the surgical techniques that have evolved are highly effective in correcting VUR. Recently, the US Food and Drug Administration (FDA) has approved an injectable implant of dextranomer/hyaluronic acid copolymer (Deflux, Q-Med, Uppsala, Sweden) for use in children, making the endoscopic treatment of reflux a potential alternative to open surgical correction [3]. This article reviews the different surgical techniques, postoperative management, and complications, as well as the various implants used in the endoscopic correction of VUR and their outcomes.

Historical roots of ureteral reimplantation

In 1952, Hutch [4] first reported the association of VUR and pyelonephritis with renal scarring in adult paraplegics. His series demonstrated that the correction of VUR in paraplegics improved hydronephrosis and prevented urinary tract infection and pyelonephritis. Society is indebted to him for the early development of the technique of ureteral reimplantation, including the importance of creating a submucosal tunnel of the ureter with detrusor muscular backing. Fortunately, it is now recognized that proper management of neurogenic bladder dysfunction in paraplegics prevents the complications his operation was intended to treat.

In 1958, Politano and Leadbetter [5] reported their series of seven children treated with ureteroneocystotomy. Paquin, Lich, Glenn and Anderson, and Cohen [6–9] reported refinements of the technique of ureteral reimplant, and their techniques have become eponymous as a tribute to their contributions in ureteral reimplantation surgery. A review of the history of the surgical treatment of VUR has been published recently [2].

In 1997, the American Urological Association's panel of the treatment of VUR published guidelines for the treatment of children with VUR [1]. This comprehensive report included a meta-analysis of all published data on the treatment of reflux. It outlines treatments as guidelines and options and states whether they are based on published evidence versus expert recommendation. Antibiotic prophylaxis is the recommended initial therapy for all children with grades I to II reflux. Only in older children (6 or more years of age) with bilateral grades III or higher was surgical correction an initial option. In all children with grades III to V reflux and persistent reflux despite a trial of observation on prophylactic antibiotics, however, surgical correction was recommended as a guideline or preferred option. Endoscopic correction was not recommended because of a lack of a safe and proven efficacious implant for injection.

Intravesical ureteral reimplantation

Intravesical ureteral reimplantation has been the standard treatment of VUR in the United States for the past half-century. Techniques can be categorized as those that require a neocystotomy or those where the ureter is advanced into the bladder through the existing ureteral hiatus. This article reviews the basic techniques of the most

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commonly performed types of ureteral reimplants, but does not provide detailed surgical descriptions of the procedures.

The surgical objective of ureteral reimplantation is to create a passive flap valve mechanism that allows the ureter to occlude temporarily while the intravesical pressure rises within the bladder, therefore preventing VUR from occurring. A mucosal tunnel with a length–to–ureteral diameter ratio of 5:1 should result reliably in success rates that exceed 95% [10]. The second goal is to allow for normal ureteral peristalsis and drainage into the bladder without obstruction.

The most commonly performed ureteral reimplant involving neocystotomy, or creation of a new ureteral hiatus, is the Politano-Leadbetter reimplant. Originally reported in 1958, many hailed this as the ideal ureteral reimplant [5,10]. The submucosal tunnel length can be varied depending on the position of the neohiatus, allowing for the reimplantation of dilated or tapered ureters. The ureter is backed by detrusor that has not been reconstructed with sutures, making the muscular support for the ureter more reliable. Finally, the ureteral orifice is positioned similar to the normal anatomic path of the ureter, ensuring that retrograde catheterization of the ureter should be accomplished readily.

The initial step in this and all intravesical ureteral reimplants involves dissection of the intravesical ureter from the detrusor and retroperitoneal attachments along the plane of Waldeyer's sheath (Fig. 1). After dissection of the ureter, the location of the neohiatus should be determined. It is important that the neohiatus be in a portion of the bladder wall that is sufficiently immobile to prevent the ureter from kinking as the bladder fills. The position of the neohiatus should be superior and medial to the original hiatus. The clamp should not be passed blindly from the neohiatus to the original hiatus, but should follow a dissection of the posterior bladder wall between the original and neohiatus, as well as dissecting the peritoneum away from the posterior bladder wall [10,11]. Failure to perform this critical maneuver risks placement of the ureter through the peritoneum and occasional intestinal injury [10,12]. A clamp is passed from the new hiatus back to the original hiatus and the ureter is pulled into the bladder at its new location. The ureter is placed through the submucosal tunnel and directed toward the bladder neck.

There are three types of ureteral advancements: (1) trigonal (Glenn-Anderson), (2) cross-trigonal (Cohen), and (3) medial advancement (Gil-Vernet). The first description of the advancement technique came from Glenn and Anderson [7], who described eight patients treated with a trigonal advancement technique. Intravesical mobilization is performed as for the Politano-Leadbetter, but from the original haitus, a submucosal tunnel is created along the course of the trigone toward the bladder neck (Fig. 2). This advances the orifice, which is often laterally ectopic, into a more normal trigonal position. The length of the submucosal tunnel achievable was described as 1.5 cm.

The main advantage of this technique is its simplicity. It eliminates the need for extravesical dissection and neocystotomy. It positions the ureter just above the bladder neck, facilitating retrograde catheterization and instrumentation if required. There are limitations to this technique, however. The trigone and ureteral orifice location must have the correct configuration for this type of reimplantation to be successful. To ensure a proper submucosal tunnel length–to–ureteral diameter ratio, this technique should not be used for significantly dilated ureters because the tunnel length is limited [7,13].

Cross-trigonal (Cohen) reimplants also require initial intravesical mobilization of the ureter, but the ureter is reimplanted across the trigone toward the contralateral ureter. Cohen's idea for this procedure came when he reimplanted two lower-pole ureters in a completely duplicated system, advancing them toward the midline to avoid mobilizing the nonrefluxing, normal, upper-pole ureters [9]. Although duplicated systems should be managed by common sheath reimplant with mobilization of both ureters, this experience inspired him to attempt to place the ureters in a cross-trigonal fashion [9,14]. The reimplantation of the ureters in this configuration creates a submucosal tunnel long enough to accommodate dilated ureters or tapered ureters (Fig. 3). Tunneling across the intact posterior bladder wall provides solid muscular backing [11,15–17].

This technique is a simple and reliable method for surgically correcting all grades of reflux. It is simpler to learn and perform than the Politano-Leadbetter reimplant, and therefore probably safer for less-experienced surgeons. The only disadvantage is the placement of the ureters out of their normal anatomic alignment, which may increase difficulty with retrograde catheterization of the ureter should it be required subsequently for treatment of urolithiasis. In the 25 years since the cross-trigonal technique was introduced, no

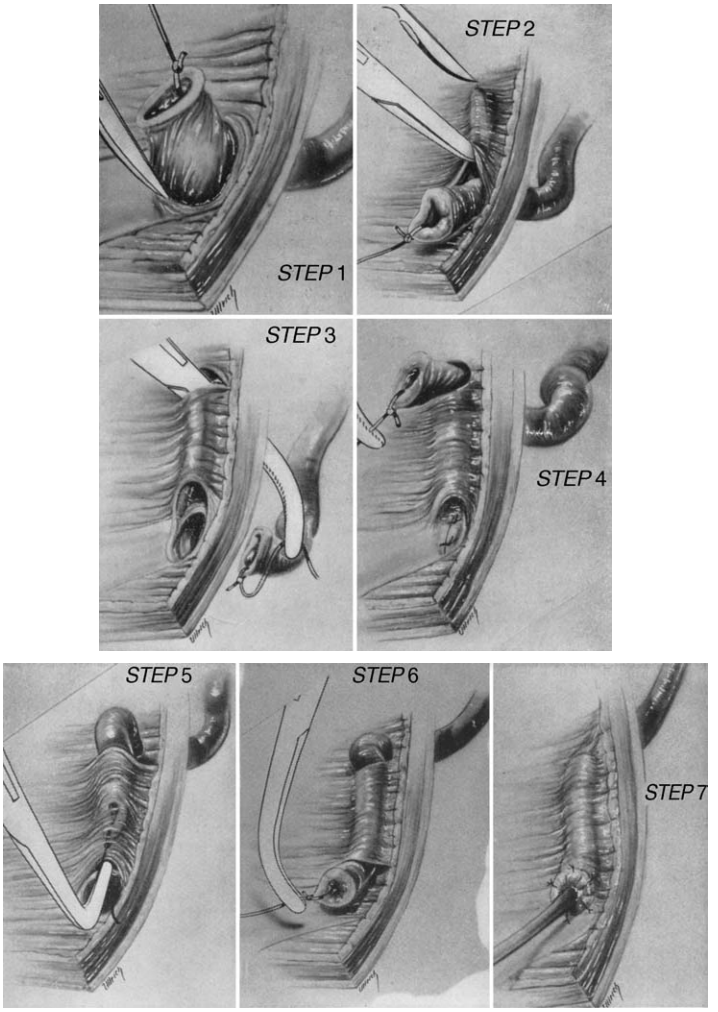


Fig. 1. Politano-Leadbetter ureteroneocystotomy. The ureter is mobilized intravesically (*Step 1*). The submucosal tunnel is created and the neocystotomy is performed (*Steps 2–3*). The ureter is brought through the neocystotomy and the original hiatus is closed (*Steps 4–6*). The ureter is passed under the submucosal tunnel and the ureterovesical anastomosis is completed (*Step 7*). (*Reproduced from* Politano VA, Leadbetter WF. An operative technique for the correction of vesicoureteral reflux. J Urol 1958;79:932–41; with permission.)

publications have supported the concern with difficult retrograde catheterization.

The midline advancement (Gil-Vernet) is a simple and rapid technique for the correction of VUR (Fig. 4). This technique is only suitable for ureters that are highly mobile intravesically. The mucosa between the ureteral orifices is incised in a transverse fashion. Mucosa is elevated off the detrusor muscle of the trigone in the bladder base. A nonabsorbable 3-0 nylon mattress suture, including Waldeyer's sheath and the intrinsic musculature of the ureter, is placed and tied, bringing the ureters to the midline. Care should be taken not to perforate the ureter because the permanent suture would act as a foreign body and likely result in stone formation. The permanent suture is buried by approximating the mucosa over it. In Gil-Vernet's original series he reported success in 36 of 38 (94%) patients [18].

Extravesical reimplantation

The extravesical ureteral reimplant was developed simultaneously and described by Lich and Gregoir [2,8]. The original description involved performing a midline cystotomy and placing

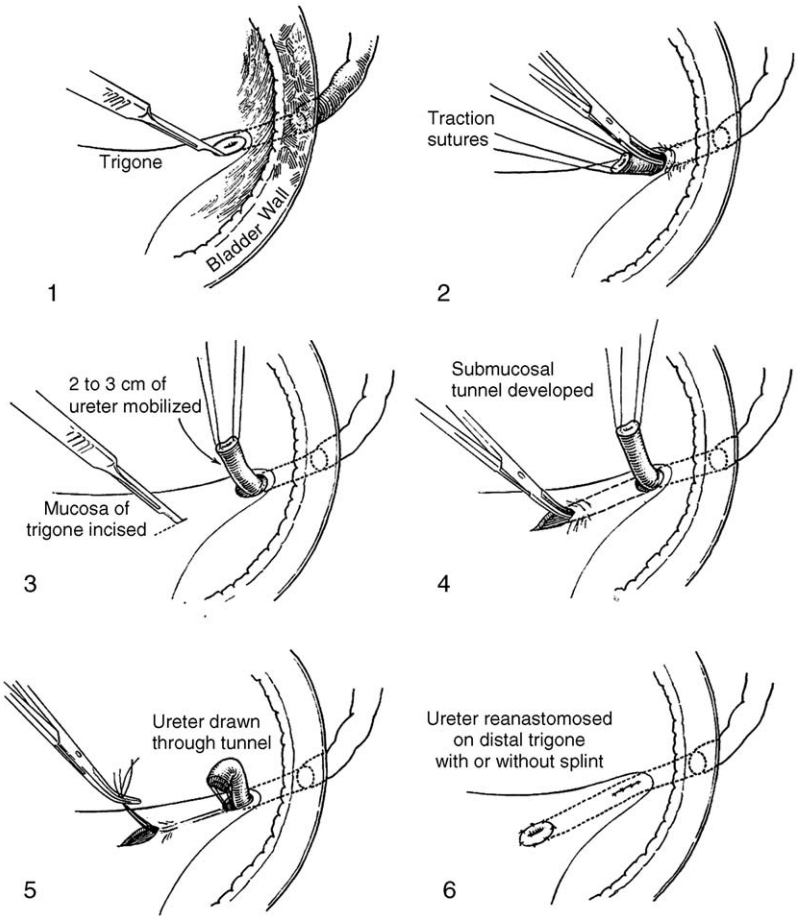


Fig. 2. Glenn-Anderson ureteral reimplant. After mobilization of the ureter (*Steps 1–3*), a submucosal tunnel is created along the trigone toward the bladder neck (*Step 4*). The ureter is passed through the submucosal tunnel and reanastomosed to the bladder (*Steps 5–6*). (*Reproduced from* Glenn JF, Anderson EE. Distal tunnel ureteral reimplantation. J Urol 1967;97:623–6; with permission.)

ureteral catheters. Following this, dissection of the ureters extravesically was performed to the region of the ureterovesical junction. The detrusor was incised laterally in a course along the natural path of the ureter, leaving the underlying mucosa intact. The trigonal attachments to the ureter were maintained. The detrusor is then sutured closed over the ureter, creating a longer submucosal tunnel. Modification of this technique in Europe involved making the detrusorotomy toward the dome of the bladder. In a large series of patients, this technique performed in a unilateral or a staged bilateral fashion had high success rates and low morbidity [19]. This technique initially was avoided in the United States following early reports of significantly higher failure rates versus intravesical ureteral reimplantation, but in the last two decades there has been a renewed interest [20–23]. Much of this enthusiasm followed the report of a modification of this technique that combines the extravesical reimplant with ureteral advancement, and is referred to as the *detrusorrhaphy* [20].

The detrusorrhaphy, like the original extravesical reimplant, involves dissecting the ureter down to the ureterovesical junction. The ureter is detached completely from the detrusor muscle fibers circumferentially, leaving only the mucosal attachments connecting the ureter to the bladder. As shown in Fig. 5, the ureter is attached only by the mucosa of the bladder and the detrusor incision is extended down toward the bladder neck to create space for advancement of the

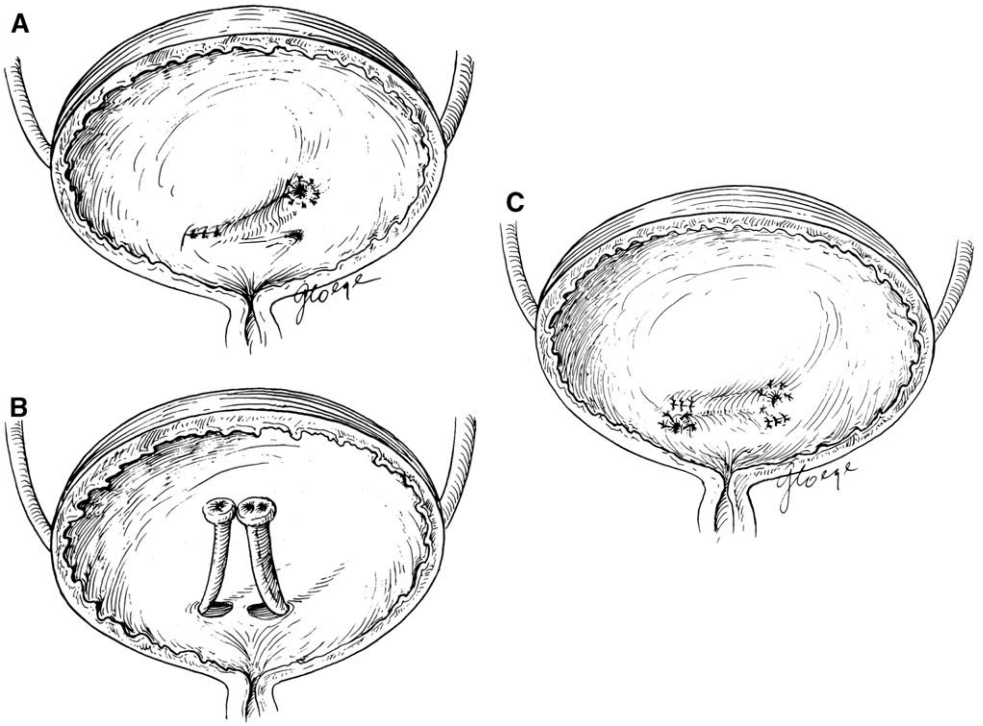
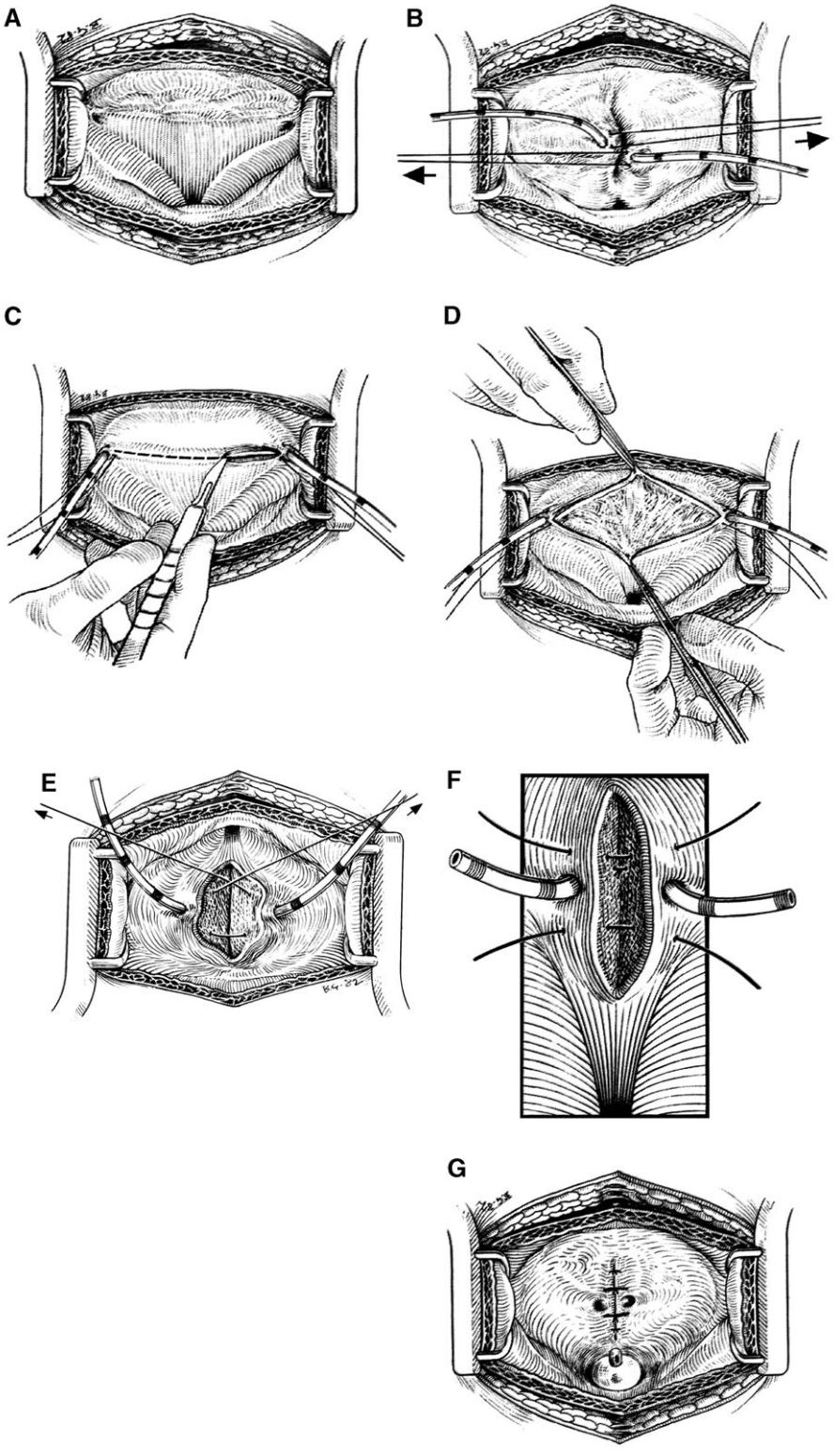


Fig. 3. Cohen ureteral reimplant. (*A*) The ureters have been mobilized intravesically (left ureter is duplicated). Submucosal tunnels are created across the trigone bilaterally (*B*), and the ureters are reimplanted (*C*). (*Reproduced from* Ehrlich RM. Success of the transvesical advancement technique for vesicoureteral reflux. J Urol 1982;128:554–7; with permission.)

ureter. The detrusor is incised posterior to the ureterovesical junction along the expected course of the ureter to create a sufficient length of the submucosal tunnel to prevent reflux. The length of this incision should depend on the grade of reflux and the diameter of the ureter. Vest-type sutures are placed into the ureteral musculature that advance and anchor the ureter to the apex of the detrusorotomy. The edges of the detrusor muscle are then approximated over the ureter to create the muscular backing of the submucosal tunnel. Both techniques have excellent results in terms of reflux resolution. The extravesical approach is amenable to reimplantation of single or duplicated ureters [23]. Paraureteral diverticuli can be repaired by the extravesical approach as well [24]. Transient hydronephrosis may develop in a small percentage of patients, but obstruction requiring reoperative reimplantation is extremely rare [49]. The most notorious complication of extravesical ureteral reimplantation is urinary retention when performed in a simultaneous, bilateral fashion. Table 1 compares the different intra- and extravesical techniques.

The risk for voiding difficulty following bilateral extravesical ureteral reimplantation is between 4% and 15% of patients [20–27]. Voiding difficulty is defined as urinary retention requiring intermittent or continuous catheterization beyond the normal postoperative time for catheter removal. This complication is one of the major deterrents preventing pediatric urologists from performing bilateral extravesical ureteral reimplantation.

Recently, an animal model has demonstrated a possible neurophysiologic basis for this complication [28]. The study was based on prior anatomic dissections of human cadavers demonstrating that the pelvic plexus is situated dorsomedial to the ureterovesical junction and extends toward the bladder neck [29]. Thus, dissection in the detrusor near the ureterovesical junction could injure the nerve fibers leading to the bladder. In a porcine model, unilateral mobilization of the ureter within 1 cm from the ureterovesical junction can produce unilateral loss of contractility of the bladder. Additionally, there was a greater than 50% decrease in the amount of pressure generated with stimulation of the motor nerves of the bladder [28].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In an effort to decrease the rate of postoperative voiding difficulty, a modified, inverted-Y dissection of the ureter, not dividing the muscle fibers attaching the ureter to the trigone completely, has been compared with the circumferential mobilization of the ureter [30]. In this study comparing 220 patients undergoing bilateral extravesical reimplant, the rate of urinary retention was 8.4% for the inverted-Y incision and 15.2% for the standard ureteral mobilization. These rates were not statistically different. As reported, the voiding dysfunction is temporary and the duration of intermittent or continuous catheterization is generally less than 2 weeks. Rarely, patients require intermittent catheterization for more than 1 month. No cases of permanent retention have been reported in patients undergoing extravesical ureteral reimplantation for primary VUR. Risk factors for urinary retention seem to be male gender, younger age (less than 2–3 years), and higher grades of reflux [26,30]. Patients with these characteristics should be followed carefully postoperatively; detailed preoperative counseling is needed to ensure parental understanding of this potential complication.

Success rates for extra- and intravescal ureteral reimplantation are similar. Rates are highest for grades I to III, with most series reporting rates of greater than 95% [9–11,13–23,31]. All techniques except Gil-Vernet still are used widely. No randomized studies have compared safety and efficacy among the choices of procedure. Experienced surgeons have reported excellent results with low complication rates. The rates are slightly lower with higher grades of reflux. No studies have shown conclusively one technique to be superior to another [1].

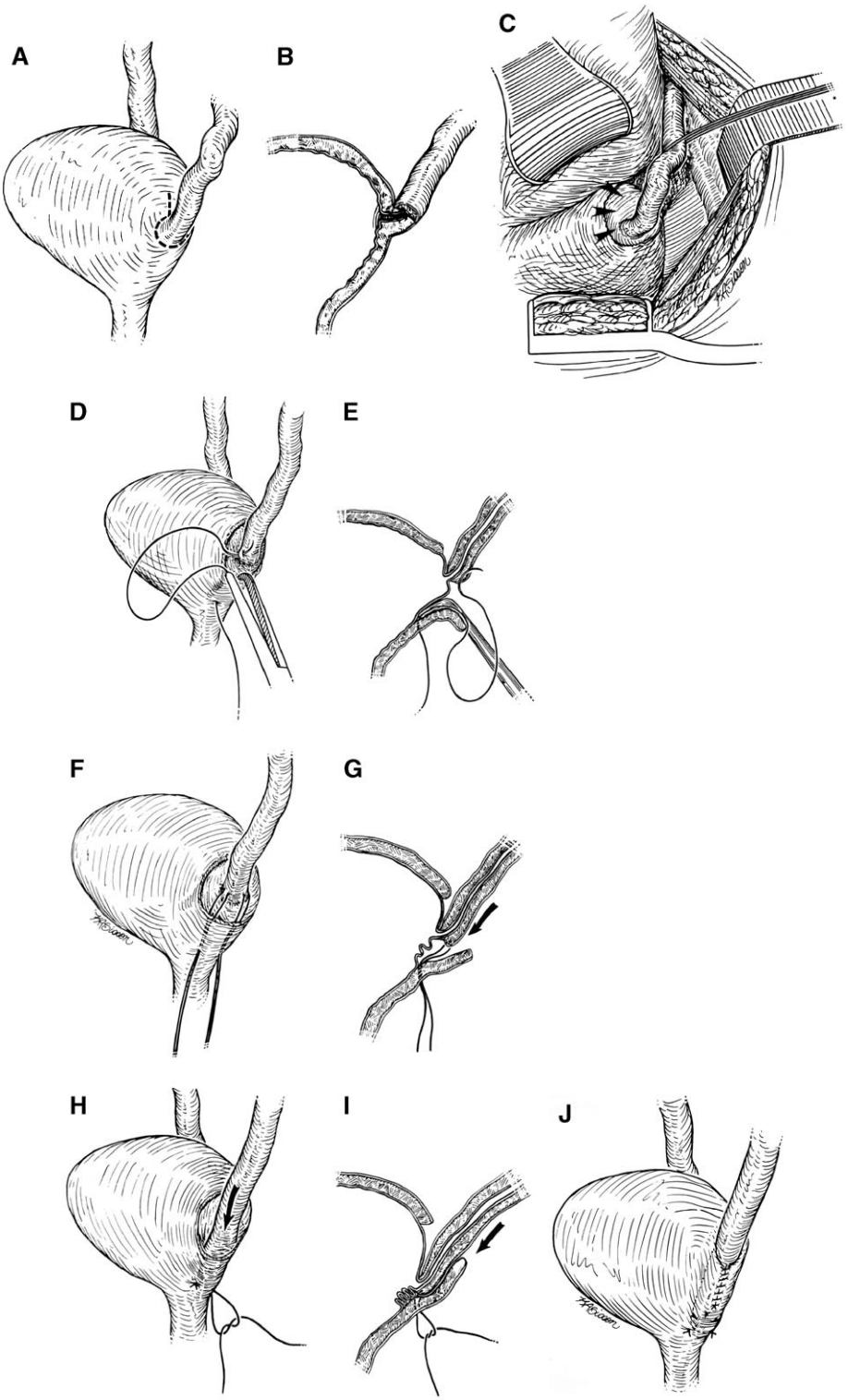
Postoperative contralateral reflux: a continued problem

A frustrating finding following an operation for unilateral reflux is de novo reflux of the contralateral ureter. Proposed etiologies for this problem include the correction of a low pressure pop-off valve (ie, the refluxing ureter that was repaired was masking the reflux by keeping the pressure in the bladder below that which would produce reflux in the contralateral side), trigonal distortion from the dissection of the reimplanted ureter (destabilization of the contralateral ureter allowing its intravesical tunnel length to decrease, resulting in reflux in a ureter that would not have previously), and failure to detect contralateral reflux preoperatively because of the intermittent nature of VUR [32–37]. Some reports indirectly support each of these theories, but none have been conclusive.

The rate of contralateral reflux is higher in patients with a history of resolved contralateral reflux. The incidence rates vary from 33% to 45% [38,39]. In one series, 100% of the de novo contralateral reflux resolved subsequently, but other series have reported only 20% resolution. Many surgeons consider it routine to reimplant a ureter that has refluxed previously because of this elevated rate of new-onset contralateral reflux [35,36,39]. Potential risk factors for the development of contralateral reflux, besides a history of prior reflux, include higher grades of reflux, duplicated system, fewer than two prior voiding cystourethrograms, and voiding dysfunction [32,36]. Reported rates of resolution for new-onset contralateral reflux (excluding ureters with prior reflux) have ranged from 50% to 100%, with most showing rates near 50% at 1 to 3 years after diagnosis.

This suggests that a conservative initial approach is reasonable. Techniques previously used to predict who will develop contralateral reflux include observing the configuration and location of the orifice at the time of reimplantation and cystoscopy to evaluate for a laterally ectopic or gaping ureteral orifice. Neither has proved useful in predicting which patients will develop contralateral reflux [34,35,40]. In an attempt to diminish the rate of new-onset reflux following unilateral reimplant, unilateral Gil-Vernet reimplants of the nonrefluxing contralateral ureter have been performed [40,41]. Essentially, this is a prophylactic reimplant. The technique was chosen to minimize complications and the additional time to mobilize the ureter. Using this technique, the rate of new onset contralateral reflux is 0% to 6%, an improvement compared with 9% to 11% rate,

Fig. 4. Gil-Vernet ureteral reimplant. The ureters are catheterized and holding sutures are placed (*A*). The ureters must be freely mobile within the bladder as shown (*B*). The mucosa is incised between the orifices (*C*) and elevated off the detrusor (*D*). A nylon horizontal mattress suture is used to advance the ureters to the midline (*F*). The mucosa is closed, burying the nylon suture (*G*). (*Reproduced from* Gil-Vernet JM. A new technique for surgical correction of vesicoureteral reflux. J Urol 1984;131;456–8; with permission.)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without the advancement in an age-matched control population in nonrandomized studies.

In one study of patients who underwent contralateral ureteral advancement and still developed reflux, all reflux resolved within 6 months, versus only 50% of those in the control group [40]. No complications were related directly to the advancement of the contralateral ureter. One must consider that a significant percentage of children will undergo an unnecessary procedure if this approach is adopted. The potential risks to which the ureter is exposed need to be weighed against the benefits in trying to prevent this relatively infrequent and often temporary complication.

Perioperative management

The management of the patient undergoing ureteral reimplantation has changed dramatically. Two-week hospital stays were reported commonly in early series [7]. Patients were managed routinely with a urethral or suprapubic catheter, ureteral stents, and surgical drain. The catheter and stents were left for several days and gradually removed. Currently, patients can be discharged routinely from the hospital on postoperative day 1 with no tubes in place [42]. Performing the procedure on an outpatient basis has been reported [43]. Earlier discharge from the hospital improves the use of hospital resources and has not resulted in unfavorable outcomes or increased risk to the patient. This approach is only relevant for uncomplicated ureteral reimplants for primary VUR.

Pain management has improved with the use of new medications such as ketorolac, which provides excellent relief of discomfort and bladder spasms. The use of local or regional blocks helps children recover quickly by providing better immediate postoperative pain relief [42,43]. Continuous epidural infusions have been used in patients with postoperative reimplantation with good pain control. A report concluded that an epidural catheter did not increase the length of stay (average length of stay 4 days for either group) [44]. If children are being discharged routinely 24 hours after surgery, however, an epidural left in likely would delay removal of the urethral catheter and increase the length of stay. A novel approach is the instillation of intravesical bupivicaine (0.25%, 0.05–0.1 mg/kg) into the bladder lumen before completion of the bladder closure [42]. In a series of patients treated using this technique, no urethral catheter was used.

The necessity of placement and timing of removal of bladder catheters has been investigated. Several investigators have concluded that a urethral catheter is not necessary after intravesical or extravesical ureteral reimplantation [42,43,45]. Certain patients undergoing bilateral extravesical ureteral reimplant (approximately 10%–15%) will not urinate spontaneously. Catheters can be placed in these patients postoperatively. In a series of 27 patients undergoing cross-trigonal ureteral reimplantation without a catheter, only 1 in 27 failed to void, and that patient had undergone reimplantation for bilateral duplex systems with excision of an ureterocele. It seems that earlier urethral catheter removal results in shorter hospital stays [46]. Postoperative stays of 24 to 48 hours with minimal or no catheter are possible without increase in morbidity. Detailed counseling and parental preparation are important in achieving the anticipated postoperative course. Investigators report that parental expectation and counseling were most important to early discharge from the hospital.

Ureteral stents and perivesical drains have been used routinely in children undergoing intravesical ureteral reimplantation. Multiple series have demonstrated that intravesical and extravesical reimplantations can be performed safely without ureteral stents [10,11,13,20–23]. There is no increased risk for hydronephrosis or obstruction in these patients [45,47]. The risk for anuria or acute renal failure in the case of bilateral ureteral reimplants is rare. One study has evaluated the characteristics of the drainage from the perivesical drain following intravesical reimplantation [48]. In 15 patients, the drainage on postoperative day 1 was consistent with serum in all. Multiple samples were evaluated before or after the urethral catheter was removed and urine was never detected. Of

Fig. 5. Detrusorrhaphy. The ureter is dissected extravesically to the detrusor muscle (*A*). The incision in the detrusor muscle is outlined (*B*). Once the muscle fibers are divided, the ureter is attached solely to the bladder mucosa circumferentially (*C*). The ureter is advanced toward the bladder neck with two sutures (*D–I*). The detrusor edges are closed over the ureter with interrupted sutures (*J*). (*Reproduced from* Zaontz MR, Maizels M, Sugar E, Firlit CF. Detrusorrhaphy: extravesical ureteral advancement to correct vesicoureteral reflux in children. J Urol 1987;138:947–9; with permission.)

Table 1
Commonly used techniques of surgical ureteral reimplantation

Author	Technique	Advantages	Disadvantages
Politano-Leadbetter	Intravesical ureteroneocystotomy	Potential for a long submucosal tunnel; anatomic alignment of the ureters for retrograde catheterization	Potential complications as a result of neocystotomy (obstruction, trans-peritoneal placement, bowel injury)
Glenn-Anderson	Intravesical trigonal advancement	No neocystotomy and anatomic alignment of ureters; simple to perform	Not suitable for dilated ureters as a result of limitation of submucosal tunnel length
Cohen	Intravesical cross-trigonal advancement	No neocystotomy and potential for long tunnel length; simple to perform	Ureters not in anatomic alignment could prevent retrograde catheterization
Gil-Vernet	Intravesical medial advancement	No neocystotomy; simple and rapid procedure because of limited dissection of ureters	Less successful than other intravesical techniques and only suitable if ureters are highly mobile within the bladder
Lich-Gregior and Zaontz and colleagues	Extravesical neocystotomy with or without advancement	Ureters in anatomic alignment; less postoperative bladder symptoms and hematuria	Difficult dissection; potential temporary urinary retention when performed bilaterally

urologists surveyed in this report, 63% of those performing extravesical, and 25% performing intravesical reimplants did not use a drain routinely. An additional 25% of those who used drains believed they were placed out of habit and unnecessary. At the authors' institution, uncomplicated ureteral reimplants are managed routinely with a urethral catheter and without ureteral stents or perivesical drains. The urethral catheter is removed early in the morning of postoperative day 1, and most children are discharged later that day.

Postoperative imaging studies

The typical radiographic evaluation of patients after ureteral reimplantation has been an upper-tract study to exclude obstruction and voiding cystourethrogram to exclude persistent or new reflux. Initially, intravenous pyelograms were performed, but more recently, series report the use of renal ultrasound to detect hydronephrosis. When hydronephrosis is discovered and persists, either a diuretic renal scan or intravenous pyelogram is performed. Studies of intra- and extravesical reimplants have reported the development of mild, transient hydronephrosis in 6% to 7% of patients [49,50]. This typically resolved in nearly all patients. The overall rate of obstruction for ureteral reimplantation requiring surgical revision is less than 1% [1]. Upper-tract imaging studies are performed typically within 6 to 12 weeks of surgery. Earlier studies are indicated in patients with decreased urine output, elevated creatinine, hypertension, or with the development of flank pain [49].

Voiding cystourethrography is an invasive test that in some children can be traumatic. Efforts to decrease the traumatic nature of this procedure include using lubricants containing local anesthetic or conscious sedation [51,52]. Neither method eliminates fear and discomfort during the procedure. In some children, catheterizations are so traumatic that parents may choose surgical correction to limit the number of voiding cystourethrograms the child must undergo while waiting for reflux to resolve [53]. The utility of postoperative voiding cystourethrograms following intra- and extravesical reimplantation has been examined [49,54,55]. Success rates of 98% to 99% for cross-trigonal reimplantations have been reported. Most children will have to undergo a negative test to detect the few who have persistent reflux. Furthermore, there is no evidence that altering the management of persistent postoperative reflux is of significant benefit to the patient.

In recent years, many pediatric urologists have adopted a practice of not performing postoperative voiding cystourethrograms routinely in patients undergoing uncomplicated ureteral reimplantation for primary VUR. Before adopting such a policy, one may want to ensure that one's surgical outcomes meet the standards published (at least a 95% success rate). The second important component to this policy is parental education and discussion. In the case of bilateral reimplants, there is low risk for postoperative reflux, but with a unilateral reimplant, the risk is significantly greater because of the onset of new contralateral reflux.

One needs to decide whether the findings of the voiding cystourethrogram would alter one's management. If antibiotics prophylaxis would be continued for persistent reflux, then postoperative voiding cystourethrograms should be performed [55]. If the surgeon's policy would be to stop prophylaxis and observe the patient expectantly, however, then omitting the voiding cystourethrogram would be reasonable. Parents and the surgeon need to agree on a comfortable level of risk when making this decision. In the case of extravesical reimplants, there is a high (95%) cure rate. The overall cure rate is higher with reflux grade III or less versus grades IV and V (99% versus 94%); thus, it has been recommended that routine cystography is necessary only for high-grade reflux (IV and V) [49]. Limiting the use of postoperative ultrasound to patients who are symptomatic or who have risk factors for developing hydronephrosis, such as dysfunctional voiding, preoperative hydronephrosis, flank pain, hypertension, or an elevated creatinine, has been proposed [50]. Nonetheless, the routine use of ultrasound seems more justified because it is noninvasive and painless and can detect a potential silent obstruction and prevent the delayed complication of significant injury to the kidney by providing early diagnosis.

Minimally invasive treatment of vesicoureteral reflux

Laparoscopic repair

Laparoscopic ureteral reimplant is a technically challenging procedure. Two distinct techniques for the intravesical repair of vesicoureteral reflux have been reported. The first reports in children were performed by medial advancement (Gil-Vernet technique) of the ureters [56]. The procedure was changed later because of high failure rates (greater than 50%) than a cross-trigonal (Cohen) technique. These techniques have not resulted in success rates comparable to the open surgery (80% with the intravesical cross-trigonal technique) [57,58].

Laparoscopic extravesical ureteral reimplantation was first reported in 1993 in an animal model [59]. A consecutive series of 47 patients and 71 ureters reimplanted since 1997 reports 100% success [60]. During the early development of this technique, ureteral injury occurred in three patients, requiring surgical revision in two. Preliminary reports have demonstrated that after bilateral laparoscopic extravesical reimplantation, there is no significant instance of voiding dysfunction compared with expected rates with open bilateral extravesical reimplant [61]. Although these techniques are not practiced widely, the last decade has seen a dramatic change in the practice of laparoscopic surgery in urology. Adult procedures once considered unsuitable for laparoscopy are now reported in large series with comparable operative times. With future improvements in instrumentation and possible use of robotic assistance, this procedure may become a more viable alternative to open surgery, especially in older children and adolescents. Because of the relatively small size of the pelvis in younger children, its role in these patients likely will be limited.

Endoscopic correction of vesicoureteral reflux

Endoscopic treatment of reflux has been practiced for the past two decades. The American Urologic Association guidelines for the treatment of VUR did not recommend endoscopic injection for the treatment of reflux because of a lack of data documenting the efficacy of this treatment and the lack of a suitable and safe implant material. The first material used was polytetrafluoroethylene, a paste of Teflon particles. Subureteric Teflon injection procedure has been used more extensively in Europe. A large multi-center series of over 8000 patients has been reported [62].

Other implants that have been used include bovine cross-linked collagen, autologous chondrocytes, dextranomer/hyaluronic acid copolymer, polydimethylsiloxane, and other substances [63]. Of the implants listed, only dextranomer/hyaluronic acid copolymer is available in the United States and approved by the FDA for use in the endoscopic correction of primary VUR, grades II to IV, in patients with single collecting systems [3]. Polytetrafluoroethylene has been favored in

Europe because of its high success rate. Polytetrafluoroethylene particles are a nonbiodegradable permanent implant. The major concern with polytetrafluoroethylene is that the particles are small enough to migrate in lymphatic channels and capillaries. Documentation demonstrates the migration of particles following injection in the urinary tract [64]. Because of safety concerns it is no longer used in the United States, but large series do not report complications related to the Teflon paste [62].

Autologous chondrocytes are a biocompatible material, circumventing the concerns about long-term problems with implants containing Teflon or silicone-based implants. The procedure involves an excisional biopsy to obtain the chondrocytes, which are expanded in vitro and suspended in an algalate solution that is injected subureterically [65]. Viable chondrocytes have not been demonstrated in patients who failed endoscopic therapy and underwent ureteral reimplantation. Whether this represents the cause of the treatment failure or the inability of the chondrocytes to survive after injection is unknown.

Glutaraldehyde cross-linked bovine collagen was developed and used widely as an injectable material for the treatment of incontinence. When injected subureterically it had a reasonable early success rate, but long-term studies have shown unacceptably high failure rates over time [66]. It is biodegradable and, because of the potential for an immune reaction against the collagen protein, patients need to undergo skin testing before implantation. Dextranomer/hyaluronic acid copolymer has been studied primarily in Europe, where it was used first. It has results that are comparable to Teflon, but the dextranomer particle size is larger, which should prevent migration [67,68]. Polydimethylsiloxane is a solid silicone elastomer suspended in a polyvinylpyrrolidone hydrogel. The hydrogel is removed by the reticuloendothelial system and excreted [69].

The technique of endoscopic injection for VUR begins with cystoscopic examination of the orifice. The use of a cystoscope with an offset lens and a straight 4–5 french working channel is important because the needle can be bent easily when passing through the offset channel of standard cystoscopes, making it difficult to position [3]. The needle is inserted a few millimeters distal and medial to the orifice, and advanced into position just under the ureter. Injection should produce a mound of implant material that elevates the ureteral orifice and causes it to assume a crescent shape. The amount injected varies with implant types. Mean volumes of 0.6 to 0.8 mL reported for dextranomer/hyaluronic acid copolymer and 0.4 mL for polytetrafluoroethylene [3,67,70]. After the injection is complete, the needle is left in place for 15 to 30 seconds before withdrawing it. The site

Table 2
Different implant materials studied for endoscopic treatment of reflux

Implant	% Reflux cured with one injection[a]	Biodegradable	Comments
Autologous chondrocytes	55%	Autologous	Requires two procedures: cartilage harvest and the subsequent subureteric injection
Bovine cross-linked collagen	72%	Yes	Skin allergy testing prior to treatment; high relapse rate after 1 y
Dextranomer/hyaluronic acid copolymer	72%	Yes	Nonimmunogenic; easy to inject with syringe and needle; only implant FDA-approved for the treatment of reflux in children in the United States
Polydimethylsiloxane	82%[b]	No	Solid silicone elastomere soft tissue bulking agent suspended in bioexcreteable carrier gel
Polytetrafluoroethylene	73%	No	Teflon particles suspended in glycerine; small particle size makes migration a concern; most studied of all implants with largest series

[a] Overall for all reflux grades.
[b] Grades I–III only.

should be inspected to ensure that the implant does not extrude and the orifice has maintained its position at the top of the mound.

Table 2 shows the agents used for implantation and reported success rates for a single injection. Success rates, as with surgical reimplantation, are higher for lower grades of reflux. Success rates varied from 98% to 83% for grades I to V reflux when treated with polytetrafluoroethylene using repeat injections for failures [62,70]. Polydimethylsiloxane and dextranomer/hyaluronic acid copolymer have similar reported rates of success rates varying from 90% to 65% for reflux grades I to V [3,67,69,71]. The long-term efficacy of preventing reflux is not well established with these agents. For the dextranomer/hyaluronic acid copolymer, most studies only performed cystograms at 3 months or 1 year from the procedure [3,67]. In studies of collagen, the high failure rate did not occur until years later [66]. For the dextranomer/hyaluronic acid copolymer, there is one long-term study with 228 patients at a median follow-up of 5 years. The overall success rate (defined as no reflux or grade I reflux) was 68% [67]. Most patients had undergone their latest cystogram 12 months postoperatively. There were 334 ureters treated, of which 45 ureters without reflux underwent a late voiding cystourethrogram at a median of 3 years postinjection, showing a recurrent reflux rate of 13%. The implant is biodegradable, but length of time for resorption is not known.

A question remains about whether patients, especially girls, may have problems with recurrent reflux in adulthood, particularly during their reproductive years. Unfortunately, no data are available regarding the efficacy of endoscopic treatment of reflux in children as they grow into adulthood. The risk of obstruction is low with endoscopic injection. Ultrasound studies have failed to show a significant rate of hydronephrosis, even when checked at postoperative day 1 [67]. Children are treated as outpatients and have little to no discomfort [3]. The typical follow-up protocol for patients is similar to that of open surgical reimplantation, with an ultrasound and cystogram performed 6 to 12 weeks following the procedure.

Summary

Surgical reimplantation remains a highly effective and safe technique for the correction of VUR. Endoscopic correction of VUR is an option as an alternative to surgical reimplantation. The morbidity and recovery from endoscopic correction of reflux is improved versus reimplantation, but is less efficacious and the long-term results into adulthood are unknown.

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Evaluation of hematuria in children

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The detection of even microscopic amounts of blood in a child's urine alarms the patient, parents, and physician, and often prompts the performance of many laboratory studies. Hematuria is one of the most important signs of renal or bladder disease, but proteinuria is a more important diagnostic and prognostic finding, except in the case of calculi or malignancies. Hematuria is almost never a cause of anemia. The physician should ensure that serious conditions are not overlooked, avoid unnecessary and often expensive laboratory studies, reassure the family, and provide guidelines for additional studies if there is a change in the child's course [1]. This article provides an approach to the evaluation and management of hematuria in a child [2,3]. Many tests have been recommended for the child with hematuria, but no consensus exists on a stepwise evaluation. Although more research is needed to resolve certain controversies in management, the suggested approach aims to detect major or treatable problems and limit the anxiety, cost, and energy required by unnecessary testing.

Definitions

Macroscopic hematuria is visible to the naked eye, but *microscopic* hematuria usually is detected by a dipstick test during a routine examination. Hematuria is confirmed by microscopic examination of the spun urine sediment. Microscopic examination is performed with concentration of the urinary sediment by centrifugation. Ten milliliters of urine is spun at 2000 rpm for 5 minutes. Nine milliliters is decanted and the sediment is resuspended and an aliquot examined. The urine is examined by microscopy by high power field (hpf) that is 400× magnification. Macroscopic hematuria often does not require concentration. Bright-red urine, visible clots, or crystals with normal-looking red blood cells (RBCs) suggests bleeding from the urinary tract. Cola-colored urine, RBC casts, and deformed (dysmorphic) RBCs suggest glomerular bleeding [4]. An absence of RBCs in the urine with a positive dipstick reaction suggests hemoglobinuria or myoglobinuria.

The sensitivity and specificity of the dipstick method for detecting blood in the urine vary. When tested on urine samples in which a predetermined amount of blood has been placed, dipsticks have a sensitivity of 100 and a specificity of 99 in detecting one to five RBCs/hpf [5]. This corresponds to approximately 5 to 10 intact RBCs/μL urine [6]. There is no consensus on the definition of microscopic hematuria, although more than 5 to 10 RBCs/hpf is considered significant [7,8]. The author and others recommend that at least two of three urinalyses show microhematuria over 2 to 3 weeks before further evaluation is performed [3,9]. The American Academy of Pediatrics recommends a screening urinalysis at school entry (4–5 years of age) and once during adolescence (11–21 years of age) as a component of well child–care.

Incidence and prevalence

Pediatricians frequently encounter hematuria in children. Macroscopic hematuria has an estimated incidence of 1.3 per 1000 [2]. Microscopic hematuria, although more common than gross

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hematuria, has a variably reported incidence depending on the definition used for making the diagnosis. The incidence of microscopic hematuria in schoolchildren was estimated at 0.41% when four urine samples per child were collected and 0.32% in girls and 0.14% in boys when five consecutive urine specimens were analyzed over 5 years [10,11]. Microscopic hematuria in two or more urine samples is found in 1% to 2% of children 6 to 15 years of age.

Pathophysiology

Hematuria may originate from the glomeruli, renal tubules and interstitium, or urinary tract (including collecting systems, ureters, bladder, and urethra) (Boxes 1 and 2). In children, the source of bleeding is more often from glomeruli than from the urinary tract. RBCs cross the glomerular endothelial-epithelial barrier and enter the capillary lumen through structural discontinuities in the capillary wall. These discontinuities seem to be at the capillary wall–mesangial cell reflections [12]. In most cases, proteinuria, RBC casts, and deformed (dysmorphic) RBCs in the urine accompany hematuria caused by any of the glomerulonephritides. The renal papillae are susceptible to necrotic injury from microthrombi and anoxia in patients with a hemoglobinopathy or in those exposed to toxins. Patients with renal parenchymal lesions may have episodes of transient microscopic or macroscopic hematuria during systemic infections or after moderate exercise. This may be the result of renal hemodynamic responses to exercise or fever by undetermined mechanisms.

Box 1. Causes of hematuria in children

Glomerular diseases
Recurrent gross hematuria (IgA nephropathy, benign familial hematuria, Alport's syndrome)
Acute poststreptococcal glomerulonephritis
Membranoproliferative glomerulonephritis
Systemic lupus erythematosus
Membranous nephropathy
Rapidly progressive glomerulonephritis
Henoch-Schonlein purpura
Goodpasture's disease

Interstitial and tubular
Acute pyelonephritis
Acute interstitial nephritis
Tuberculosis
Hematologic (sickle cell disease, coagulopathies von Willebrand's disease, renal vein thrombosis, thrombocytopenia)

Urinary tract
Bacterial or viral (adenovirus) infection–related
Nephrolithiasis and hypercalciuria
Structural anomalies, congenital anomalies, polycystic kidney disease
Trauma
Tumors
Exercise
Medications (aminoglycosides, amitryptiline, anticonvulsants, aspirin, chlorpromazine, coumadin, cyclophosphamide, diuretics, penicillin, thorazine)

Initial evaluation

Macroscopic hematuria

The evaluation of a child with gross hematuria differs from that of microscopic hematuria (Fig. 1). Macroscopic hematuria of glomerular origin usually is described as brown, tea-colored, or cola-colored, whereas macroscopic hematuria from the lower urinary tract (bladder and urethra) is usually pink or red. Macroscopic hematuria in the absence of significant proteinuria or RBC casts is an indication for a renal and bladder ultrasound to exclude malignancy or cystic renal disease. Referral to a urologist is required when clinical evaluation and workup indicates that there is a tumor, a structural urogenital abnormality, or an obstructing calculus. A urologist also should evaluate children with recurrent nonglomerular macroscopic hematuria of undetermined origin because cystoscopy may be warranted.

Microscopic hematuria

Microscopic hematuria, defined by more than five RBCs/hpf, almost always warrants referral to a nephrologist rather than an urologist. Figs. 2 and 3 give an approach to the evaluation of asymptomatic and symptomatic microscopic

Box 2. Causes of asymptomatic isolated microscopic hematuria

Common
Undetermined
Benign familial
Idiopathic hypercalciuria
IgA nephropathy
Sickle cell trait or anemia
Transplant

Less common
Alport nephritis
Postinfectious glomerulonephritis
Trauma
Exercise
Nephrolithiasis
Henoch-Schonlein purpura

Uncommon
Drugs and toxins
Coagulopathy
Ureteropelvic junction obstruction
Focal segmental glomerulosclerosis
Membranous glomerulonephritis
Membranoproliferative glomerulonephritis
Lupus nephritis
Hydronephrosis
Pyelonephritis
Vascular malformation
Tuberculosis
Tumor

(*Adapted from* Lieu TA, Grasmeder M, Kaplan BS. An approach to the evaluation and treatment of microscopic hematuria. Pediatr Clin North Am 1991;38:579–92.)

hematuria. Most children with isolated microscopic hematuria do not have a treatable or serious cause for hematuria and do not require an extensive evaluation. The presence of hematuria must be confirmed by microscopy examination of spun sediment of urine because other substances besides blood can produce red or brown urine or give a false positive dipstick test for blood (Box 3).

Once a positive dipstick result has been confirmed by microscopic examination of spun sediment of urine, it is advisable to redirect attention to more specific aspects of the history and physical examination (Box 4).

History

A history of dysuria, frequency, urgency, or flank or abdominal pain suggests a diagnosis of urinary tract infection or nephrolithiasis. Recent trauma, strenuous exercise, menstruation, or bladder catheterization may account for transient hematuria. A sore throat or skin infection within the past 2 to 4 weeks directs the evaluation toward postinfectious glomerulonephritis. Drugs and toxins may cause either hematuria or hemoglobinuria (Box 5). A careful family history must include questions about hematuria, hearing loss, hypertension, nephrolithiasis, renal diseases, renal cystic diseases, hemophilia, sickle cell trait, and dialysis or transplant.

Physical examination

The presence or absence of hypertension or proteinuria helps to decide how extensively to pursue the diagnostic evaluation. If the blood pressure is normal and the patient is passing normal amounts of urine, it is unlikely that microscopic hematuria, whatever its cause, warrants immediate treatment. If the blood pressure is elevated, the hematuria requires a more intensive diagnostic evaluation. The presence of fever or costovertebral angle tenderness may indicate a urinary tract infection. An abdominal mass may be caused by a tumor, hydronephrosis, multicystic dysplastic kidney, or polycystic kidney disease. Macroscopic hematuria with proteinuria suggests glomerulonephritis. Rashes and arthritis can occur in Henoch-Schonlein purpura and systemic lupus erythematosus. Edema is an important feature of the nephrotic syndrome (Table 1).

Laboratory studies

Only two diagnostic tests are required for a child with microscopic hematuria: (1) a test for proteinuria and (2) a microscopic examination of the urine for RBCs and RBC casts. Children with macroscopic hematuria require urine culture and renal imaging by ultrasound. Proteinuria may be present regardless of the cause of bleeding, but usually does not exceed 2+ (100 mg/dL) if the only source of protein is from the blood. This is especially true if the child has microscope hematuria. Patients with 1+ to 2+ proteinuria should be evaluated for orthostatic (postural) proteinuria. A patient with more than 2+ proteinuria should be investigated for glomerulonephritis and nephrotic syndrome. RBC casts, when present, are a highly specific marker for glomerulonephritis, but their

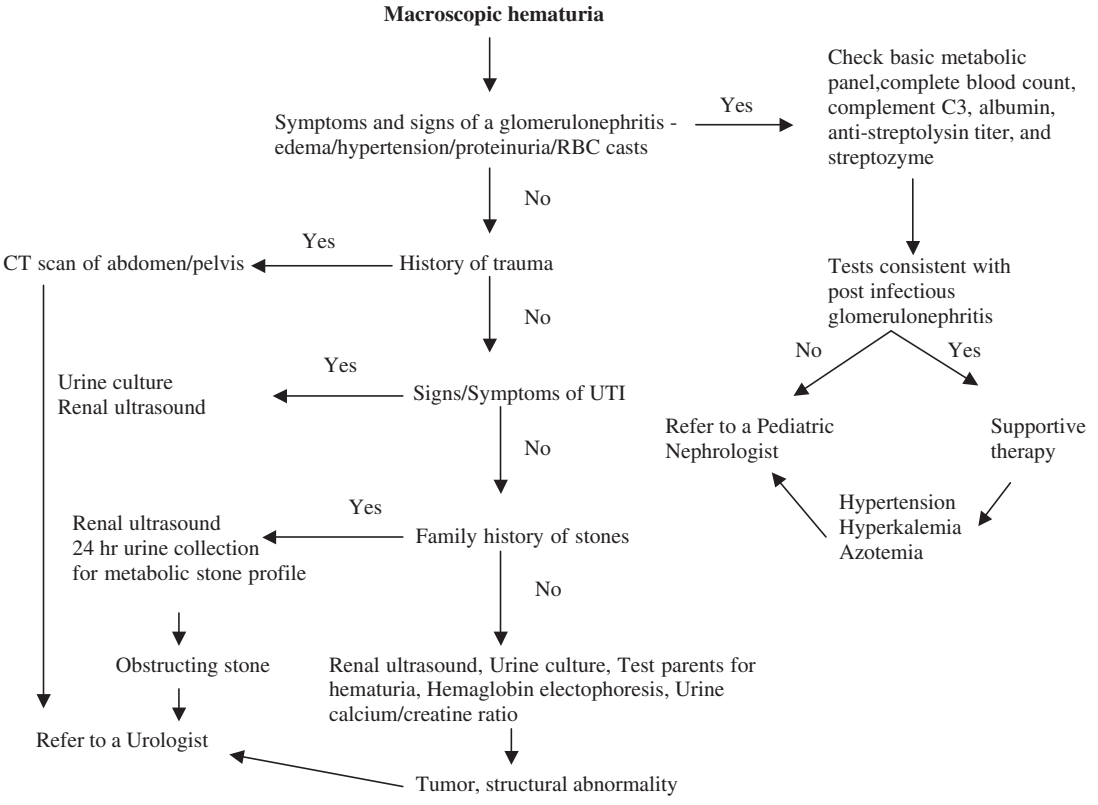

Fig. 1. Evaluation of a child with macroscopic hematuria.

absence does not rule out glomerular disease and their presence does not prove that glomerular injury has occurred. RBC casts should be searched for diligently, however. Distorted, misshapen erythrocytes (dysmorphic) also suggest a glomerular origin for bleeding.

Indications for prompt evaluation

The initial evaluation should be directed toward important and potentially life-threatening causes of hematuria in any child who has any of the following in addition to hematuria: hypertension, edema oliguria, significant proteinuria (more than 500 mg per 24 hours), or RBC casts. These causes include acute postinfectious glomerulonephritis (PIGN), Henoch-Schonlien purpura (HSP), hemolytic-uremic syndrome, membranoproliferative glomerulonephritis, IgA nephropathy, and focal segmental glomerulosclerosis.

This initial evaluation should include a complete blood count (hemolytic-uremic syndrome), throat culture, streptozyme panel and serum C3 concentration (acute poststreptococcal glomerulonephritis), and serum creatinine and potassium concentrations (if there is renal insufficiency). All children with macroscopic hematuria require renal ultrasound upon presentation. Pending the results of these tests, the child's blood pressure and urine output must be monitored frequently.

If the cause of the hematuria remains unclear after the results of the above tests have been obtained, a 24-hour urine collection for protein, creatinine, and calcium should be obtained. Children with microhematuria and protein excretion of less than 25 mg/dL (6 mg/h/m^2) usually do not have a glomerulopathy and can be considered to have isolated microscopic hematuria. Some, however, may have IgA nephropathy, early or mild Alport's syndrome, or thin basement membrane disease. There is no specific treatment, however, for any of these conditions. The causes of microscopic hematuria with substantial proteinuria include minimal change nephrotic syndrome, IgA nephropathy, Alport's syndrome, membranoproliferative glomerulonephritis, membranous nephropathy, and

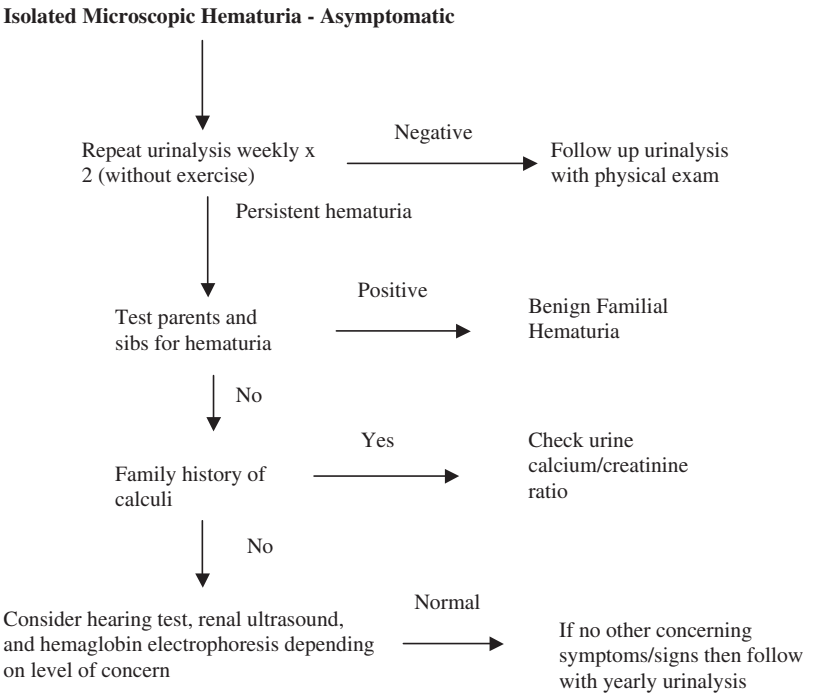
Isolated Microscopic Hematuria - Asymptomatic
Repeat urinalysis weekly x 2 (without exercise)
Negative
Follow up urinalysis with physical exam
Persistent hematuria
Test parents and sibs for hematuria
Positive
Benign Familial Hematuria
No
Family history of calculi
Yes
Check urine calcium/creatinine ratio
No
Consider hearing test, renal ultrasound, and hemaglobin electrophoresis depending on level of concern
Normal
If no other concerning symptoms/signs then follow with yearly urinalysis

Fig. 2. Evaluation of a child with asymptomatic microscopic hematuria.

focal segmental glomerulosclerosis. Additional investigations are warranted in this context, some may require treatment, and referral to a pediatric nephrologist should be considered.

Differential diagnosis and management of macrohematuria

Macroscopic hematuria requires prompt evaluation to exclude potentially life-threatening causes. A urinalysis must be performed to confirm the presence of RBCs and to look for casts and crystals. Occasionally, *Schistosoma hematobium* is diagnosed by finding ovae in the urine of an immigrant child with unexplained macroscopic hematuria [16]. Painful gross hematuria usually is caused by infections, calculi, or urologic conditions. Glomerular causes of hematuria are painless. The most common glomerular causes of gross hematuria in children are poststreptococcal glomerulonephritis and IgA nephropathy.

A detailed history must be obtained to elicit the cause of hematuria. An antecedent sore throat, pyoderma, or impetigo proteinuria, edema, hypertension, or RBC casts suggests glomerulonephritis. If the antistreptolysin O titer, streptozyme test, and serum C3 concentration are informative, the diagnosis is poststreptococcal glomerulonephritis. If these tests are not informative, further investigations are warranted to rule out other causes of glomerulonephritis. IgA nephropathy can cause recurrent macroscopic hematuria with flank or abdominal pain and may be preceded by an upper respiratory tract infection.

Fever, dysuria, and flank pain with or without voiding symptoms suggests a urinary tract infection, which is the most common cause of gross hematuria in children presenting to an emergency room. A CT scan of the abdomen and pelvis must be obtained promptly with a history of abdominal trauma and the child must be referred to a urologist. A family history of renal calculi or severe renal colic with gross hematuria suggests urinary calculi. Hypercalciuria can cause recurrent macroscopic or microscopic hematuria in the absence of calculi on imaging studies. If no obvious cause is found for macroscopic hematuria by history, physical, and preliminary studies, the differential diagnosis includes hypercalciuria, sickle cell trait, thin basement membrane disease, calculi, and vascular or bladder pathology.

Cystoscopic examination in children rarely reveals a cause for hematuria but should be done when bladder pathology is a consideration.

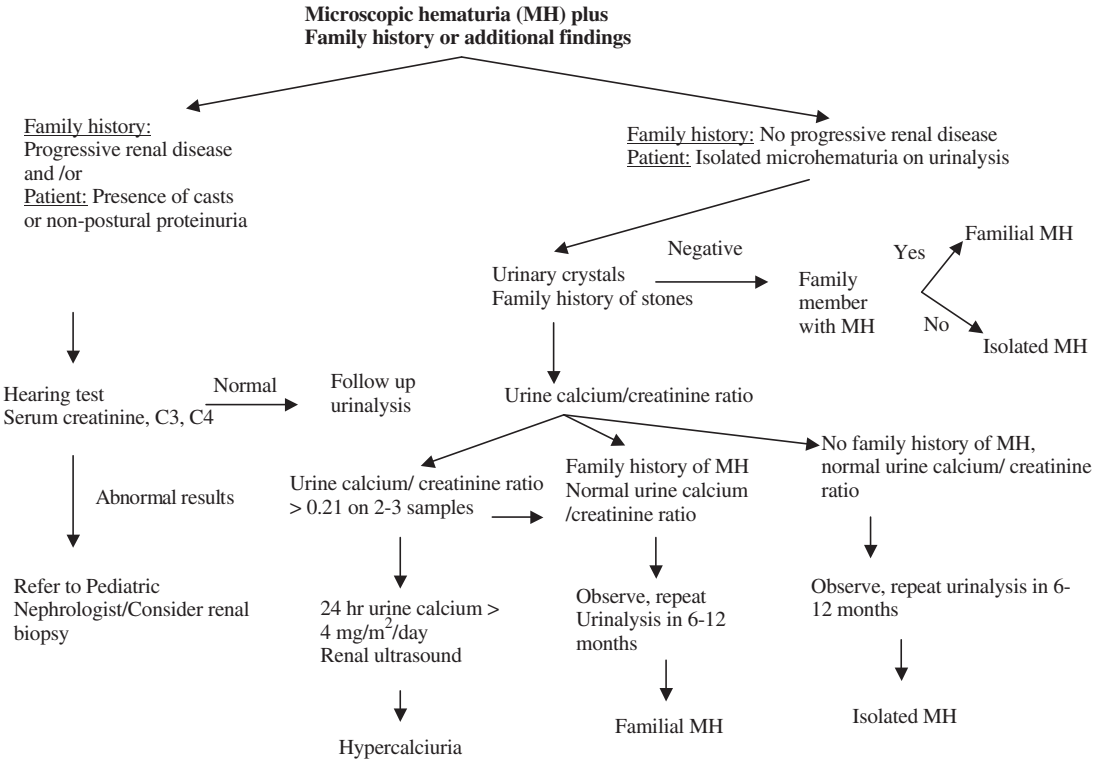

Fig. 3. Evaluation of a child with symptomatic microscopic hematuria.

Cystoscopy to lateralize the source of bleeding is performed best during active bleeding. In young girls with recurrent gross hematuria, it is important to inquire about a history of child abuse or insertion of a vaginal foreign body; the genital area must be examined for signs of injury.

Differential diagnosis of transient microhematuria

Blunt abdominal trauma may cause either microscopic or gross hematuria. Hematuria after minor blunt abdominal trauma may serve as a marker for congenital anomalies. In a study of suspected isolated renal trauma, 11 of 78 children had congenital anomalies, but only two required later surgical intervention [17]. A diagnostic study should be done only if there are at least 50 RBCs/hpf, however. Although intravenous urography traditionally has been the study of choice for suspected, isolated, blunt renal trauma, renal ultrasonography may be adequate if there are no other indications for immediate surgical intervention. Children with less than 50 RBCs/hpf are unlikely to have injuries or congenital anomalies that require intervention [17,18]. Transient hematuria may be associated with strenuous exercise. The type of activity, as well as activity duration and intensity, contributes to its development [19,20]. If the hematuria disappears with rest, no further investigation is needed.

Differential diagnosis of persistent microhematuria

The precise frequencies of occurrence of the causes of persistent microscopic hematuria have not been established. Most series have included patients with macroscopic and microscopic hematuria as well as patients with and without proteinuria. In a study of 33 children with persistent microscopic hematuria, 27 did not have proteinuria. Two of these had ureteropelvic junction obstruction, and renal biopsies were done in 21 of the remaining 25 patients, two of which had IgA nephropathy, one had hereditary nephritis, eight had normal renal biopsies, and 10 had nonspecific abnormalities [21].

The author retrospectively studied 325 children with isolated persistent microscopic hematuria

Box 3. Urine color

Dark yellow or orange
Normal concentrated urine
Rifampin pyridium

Dark brown or black
Methemoglobinemia
Bile pigments
Homogentesic acid, thymol, melanin, tyrosinosis, alkaptonuria
Alanine, cascara, resorcinol

Red or pink urine
RBCs, free hemoglobin, myoglobin, porphyrins
Benzene, chloroquine, desferoxamine, phenazopyridine, phenolphthalein
Beets, blackberries, red dyes in food
Urates

Box 4. Specific history and physical examination in a patient with hematuria

History
Trauma (recent bladder catheterization, blunt abdominal trauma)
Exercise
Menstruation
Recent sore throat, skin infection
Viral illness
Dysuria, frequency, urgency, enuresis
Urine color; stream discolored at initiation, throughout, or at termination of micturition
Abdominal pain, costovertebral angle pain, suprapubic pain
Medications (eg, cyclophosphamide), environmental toxins, or herbal compounds
Passage of a calculus
Joint or muscle pain

Family history
Hematuria
Deafness
Hypertension
Coagulopathy
Hemoglobinopathy
Calculi
Renal failure, dialysis, or transplant

Physical examination
Fever, arthritis, rash
Blood pressure
Edema
Nephromegaly
Costovertebral angle tenderness

(*Adapted from* Lieu TA, Grasmeder M, Kaplan BS. An approach to the evaluation and treatment of microscopic hematuria. Pediatr Clin North Am 1991;38:579–92.)

referred to the pediatric nephrology outpatient clinics at the Children's Hospitals of Buffalo and Philadelphia between 1985 and 1994. Hypercalciuria was present in 11%. Renal ultrasonography and voiding cystourography (VCUG) was performed in 87% and 24% of children. There were no clinically significant findings. Primary physicians or urologists ordered 75% of the VCUG before referral to a nephrologist [22]. In another study, 2 of 15 patients with persistent microscopic hematuria progressed to end-stage renal failure (one with Alport's syndrome after 14 years and one with focal segmental glomerulonephritis after 10 years), but it is not clear when in their courses these patients developed proteinuria. This study supports the author's minimalist approach to children with isolated persistent microscopic hematuria (see Fig. 2). Because the most common diagnoses in children with persistent microscopic hematuria without proteinuria are benign persistent or benign familial hematuria, idiopathic hypercalciuria, IgA nephropathy, and Alport's syndrome, a more extensive evaluation is indicated only when proteinuria or other indicators are present (see Fig. 3).

Management of microhematuria

When there are no indications for immediate intervention, the parents should be reassured that there are no life-threatening conditions, that there is time to plan a stepwise evaluation, and that most causes of isolated microscopic hematuria in children do not warrant treatment. In the author's experience, parents have two main concerns when they learn that their child has microscopic hematuria: (1) will chronic kidney damage occur, and (2) does my child have cancer (or leukemia)? Addressing these fears allays concerns and expen-

Box 5. Drugs and toxins associated with urine dipsticks positive for blood

Hemoglobinuria
Carbon monoxide
Mushrooms
Naphthalene
Sulfonamides
Tin compounds
Lead
Methicillin
Phenol
Sulfonamides
Turpentine
Ticlodipine [14]

Hematuria
Amitriptylene
Anticoagulants
Aspirin
Chlorpromazine
Cyclophosphamide
Toluene [13]
Ritonavir, indinavir [15]

(*Adapted from* Lieu TA, Grasmeder M, Kaplan BS. An approach to the evaluation and treatment of microscopic hematuria. Pediatr Clin North Am 1991;38:579–92.)

sive investigations. The plans for further testing and follow-up should be stated clearly from the outset. The dipstick and microscopic urinalysis should be repeated twice within 2 weeks after the initial specimen. If the hematuria resolves, no further tests are needed. If hematuria persists, with more than five RBCs/hpf and no evidence of hypertension, oliguria, or proteinuria on at least two of three consecutive samples, determination of the serum creatinine concentration is reasonable.

Renal ultrasonography should be considered as a screening test because it is noninvasive and provides tangible information on the presence or absence of stones, tumors, hydronephrosis, structural anomalies, renal parenchymal dysplasia, medical renal disease, inflammation of the bladder, bladder polyps, and posterior urethral valves. The yield of renal ultrasonography for evaluation of an asymptomatic child with microscopic hematuria remains unproven [22]. The value of a normal renal ultrasonographic examination in terms of reassurance, however, may justify its cost and time.

In the author's view, intravenous urography is of little value in the evaluation of persistent microscopic hematuria because renal ultrasonography is as reliable as intravenous urography for excluding macroscopic lesions. If the serum creatinine concentration and blood pressure are normal, it is reasonable to defer further investigations in an asymptomatic child with persistent microscopic hematuria who does not have hypertension, proteinuria, or RBC casts. The author suggests a follow-up examination at least every 12 months that includes microscopic urinalysis, a dipstick test for proteinuria, and blood pressure measurement.

In a study of 142 children with microscopic hematuria on two initial urine samples who had two subsequent urinalyses performed in the subsequent 4 to 6 months, 33 (23%) had persistent hematuria on both follow-up specimens [21]. The parents' urine should be tested with dipsticks [23,24]. Although phase-contrast microscopy and size-particle discrimination can distinguish glomerular from nonglomerular sources of hematuria, identification of dysmorphic RBC offers little additional information in the evaluation of microscopic hematuria in children. A thoughtful history and physical examination with microscopic urinalysis and dipstick for proteinuria provide equal diagnostic information. The author cannot recommend its routine use in the evaluation of microscopic hematuria in children [25,26].

Many other tests may be considered in the asymptomatic child with persistent microscopic hematuria, but the cost and time required for further testing must be weighed against the potential benefits, which are subjective and depend on how much importance the parents and physician place on establishing a more definite diagnosis and prognosis. These considerations apply especially to the advisability of performing a kidney biopsy on a patient with isolated microhematuria. Piqueras and colleagues [27] reviewed the clinical and renal biopsy findings in 322 children in whom nonglomerular causes of hematuria were excluded. Isolated microscopic hematuria was present in 155 children, 100 of whom had a thin basement membrane (TBM) or Alport's syndrome, 12 (7%) had IgA nephropathy, and 43 (28%) had normal or clinically insignificant glomerular findings. No child required therapy, but the argument was made that a precise diagnosis is required for prognosis, insurance purposes, and genetic counseling. In the author's opinion, renal biopsy should be deferred for this reason unless a specific indication exists.

Table 1
Distinguishing features of glomerular and nonglomerular hematuria

Feature	Glomerular hematuria	Nonglomerular hematuria
History		
Burning on micturition	No	Urethritis, cystitis
Systemic complaints	Edema, fever, pharyngitis, rash, arthralgias	Fever with urinary tract infections severe pain with calculi
Family history	Deafness in Alport's syndrome, renal failure	Usually negative; may be positive with calculi
Physical examination		
Hypertension	Often present	Unlikely
Edema	May be present	No
Abdominal mass	No	Important with Wilms' tumor, polycystic kidneys
Rash, arthritis	Lupus erythematosus, Henoch-Schonlein	No
Urine analysis		
Color	Brown, tea, cola	Bright red
Proteinuria	Often present	No
Dysmorphic red blood cells	Yes	No
Red blood cell casts	Yes	No
Crystals	No	May be informative

Isolated microscopic hematuria in the absence of a family history of hematuria in a close relative and episodes of macroscopic hematuria is unlikely to be associated with abnormal renal biopsy findings. The main exceptions are IgA nephropathy and TBM nephropathy, but there are no specific treatments for these conditions.

Specific conditions

This section focuses on the more common causes of hematuria in children and is organized according to the anatomic location for the bleeding. Box 6 outlines a suggested approach for referral of a child with hematuria.

Glomerular causes of hematuria

Postinfectious glomerulonephritis

Patients with acute PIGN often present with acute onset of tea-colored urine (macroscopic hematuria) consistent with glomerular bleeding, but the hematuria occasionally may be only microscopic [28]. Patients with PIGN may be asymptomatic or they may complain of malaise, headache, nausea, vomiting, abdominal pain, and oliguria. The physical examination may reveal edema and an elevated blood pressure that can be severe enough to cause encephalopathy. PIGN is accredited most commonly to pharyngitis or skin infection with Group A beta-hemolytic streptococci.

Clinical features of the nephritis manifest 7 to 21 days after the preceding infection. Antistreptolysin O titers may be negative early in the course, but the

Box 6. A suggested approach for referral of a child with hematuria

Nephrologist
Acute poststreptococcal glomerulonephritis if the patient has hypertension, azotemia, or hyperkalemia
Other forms of glomerulonephritis (particularly if the patient has proteinuria, hypertension, or persistent hypocomplementemia)
Family history of renal failure
Systemic disease

Urologist
Reassurance
Abnormal genitourinary anatomy
Trauma
Stones (nephrologist for metabolic work-up)
Tumor
Nonglomerular gross hematuria

streptozyme test is often positive within 10 days of the onset of symptoms [29]. Almost all patients have decreased levels of C3 early in the clinical course that normalize 6 to 8 weeks later. The C4 concentration is usually normal or only slightly decreased. If the C3 is persistently low, the patient should be further investigated for other causes of a persistent hypocomplementemic glomerulonephritis, including membranoproliferative glomerulonephritis, systemic lupus erythematosus, and chronic bacteremia. Urinalysis typically reveals RBC casts and proteinuria. Blood urea nitrogen and creatinine can be normal or elevated. In most patients hematuria and proteinuria resolves within a few weeks. Microscopic hematuria may persist for as long as 2 years. The prognosis is excellent. There are no data that indicate an untoward outcome of PIGN in a patient whose only manifestation was microscopic hematuria.

Henoch-Schonlein purpura

Approximately half of children with a clinical diagnosis of HSP manifest renal involvement [30]. Renal manifestations include hematuria, proteinuria, nephrotic syndrome, glomerulonephritis, and acute renal failure. Hematuria and proteinuria are usually transient but may persist for several months. Relapses and remissions are seen during the course of the disease and may manifest with episodes of gross hematuria. The long-term prognosis of HSP directly depends on the severity of renal involvement. In an unselected population of children with HSP, an estimated 2% develop long-term renal impairment [31]. This figure is considerably higher in specialized pediatric centers [32]. All patients with HSP who have renal involvement should be referred to a pediatric nephrologist.

IgA nephropathy

IgA nephropathy is probably the most common cause of hematuria in children [33]. The condition is diagnosed by histopathologic demonstration of mesangial deposition of IgA. IgA nephropathy usually is detected after periods of gross hematuria that follow minor infections [34]. Microscopic hematuria may be present between episodes of gross hematuria. In a school-screening program in Japan, dipstick urinalysis detects most children with microscopic hematuria who have IgA nephropathy on renal biopsy [35]. Predictors of a poorer outcome include crescentic glomerulonephritis and an older age of onset, hypertension, and nephrotic range proteinuria. There is also evidence suggesting that recurrent bouts of macroscopic hematuria predict a more guarded outcome in IgA nephropathy [36]. The prognosis of IgA nephropathy varies, and up to one third of children have a guarded long-term renal prognosis [37]. There is no specific treatment for IgA nephropathy and no evidence supports the need to make a definitive diagnosis in a child whose only manifestation is microscopic hematuria. The author disagrees with Schena's [38] and Piqueras's [39] recommendation that a renal biopsy should be done in patients with microscopic hematuria and suspected IgA nephropathy to confirm the diagnosis and to increase awareness of the prognosis of patients with IgA nephropathy in the Western world. In a few patients, IgA nephropathy may be inherited, and has been localized to 6q22-23 [40,41].

Rapidly progressive glomerulonephritis

Rapidly progressive glomerulonephritis presents with symptoms and signs similar to PIGN, and although uncommon, requires the urgent attention of a pediatric nephrologist. Laboratory studies show acute renal failure, and renal biopsy demonstrates glomerular crescents. Untreated RPGN can result in end-stage renal disease (ESRD) in a few weeks. Many of the causes of glomerulonephritis listed in Fig. 1 can present with rapid progression, or RPGN can be idiopathic [42]. Prompt diagnosis and pulsed methylprednisolone therapy may prevent progression to ESRD [43].

Alport hereditary nephritis

Alport's syndrome is a progressive, inherited glomerulonephritis accounting for 1% to 2% of patients who develop ESRD, with an estimated gene frequency of approximately 1 in 5000 [44]. Alport's syndrome is characterized by episodes of recurrent or persistent microscopic hematuria, occasionally gross hematuria, proteinuria, progressive renal insufficiency, and progressive, high-frequency, sensorineural hearing loss. The phenotype and the course vary widely. Ocular defects include anterior lenticonus and yellow-white to silver flecks within the macular and midperipheral regions of the retina [45]. Hematuria that is usually microscopic is the usual initial finding in children. In the absence of RBC casts or proteinuria, the diagnosis may be delayed or unsuspected, but this does not have serious consequences for the child unless there are hearing problems.

A careful family history and urine examinations must be obtained in every patient who

presents with microscopic hematuria. If there is any reason to suspect familial renal disease, a hearing test should be done to prevent speech or educational handicap. Men manifest signs and symptoms earlier than women, and approximately 30% can progress to ESRD. Patients who receive a renal allograft have a small risk for developing Goodpasture disease posttransplant [46]. Some women may have a hearing deficit without any urinary abnormalities. Alport's syndrome is a genetically heterogeneous disease, usually is inherited as an X-linked semidominant trait, caused by mutations in *COL4A5* gene on the X-chromosome, and in less than 10% of cases is caused by mutations of the *COL4A3* or the *COL4A4* gene on chromosome 2q.

Thin glomerular basement membrane nephropathy

Thin basement membrane nephropathy (TBMN) or *benign familial hematuria* is the most common cause of persistent glomerular bleeding in children and occurs in at least 1% of the population [47]. Benign familial hematuria may be inherited in an autosomal dominant or autosomal recessive manner, and may be associated with mutations in type IV collagen [48,49]. Proteinuria, progressive renal insufficiency, hearing deficits, or ophthalmologic abnormalities almost never occur in patients with TBMN or their family members [50]. The hematuria is usually microscopic, the RBCs may be dysmorphic, and there may be RBC casts. Occasionally, frank hematuria may occur with an upper respiratory tract infection. The histopathologic changes are thinning of glomerular basement membranes. A renal biopsy is warranted in TBMN only if there are atypical features, or if IgA disease or X-linked Alport's syndrome cannot be excluded clinically [47].

Renal parenchymal cauises of hematuria

Tumors

Children with Wilms' tumor most commonly present with flank mass or macroscopic hematuria. Although a tumor is listed frequently in the differential diagnosis of hematuria, neither the author's search of the literature nor the author's experience has produced documented cases of tumors presenting with isolated microscopic hematuria. Bladder tumors usually manifest with voiding difficulties or occasionally with macroscopic hematuria [51].

Nephrocalcinosis

Nephrocalcinosis implies an increase in calcium content in the kidney and is distinct from urolithiasis, although the two conditions often coexist. Nephrocalcinosis may be focal, occurring in an area of previously damaged parenchyma, or generalized. It is often associated with hypercalciuria. The most frequent cause of nephrocalcinosis is prematurity with and without furosemide treatment [52]. Nephrocalcinosis associated with hyperoxaluria involves the cortex and medulla, whereas the corticomedullary junction is involved most often with metabolic disease. The clinical manifestations of nephrocalcinosis include abdominal pain, dysuria, incontinence, and urinary tract infection in more than one third of patients. Microscopic hematuria usually occurs in the context of hypercalciuria or coexistant renal stone disease [53]. The diagnosis of nephrocalcinosis usually is made by renal ultrasonography [54]. The offending agent (loop diuretic, excess vitamin D) must be withdrawn if possible, and any underlying disorder (distal renal tubular acidosis) must be treated. Nephrocalcinosis rarely progresses to end stage renal failure.

Interstitial nephritis

Interstitial nephritis in children with associated microscopic or macroscopic hematuria is uncommon. Analgesics and antibiotics are implicated most frequently with resolution occurring after discontinuation of the offending medication [55,56].

Cystic renal disease

Cysts often are discovered incidentally after mild trauma or when abdominal ultrasound is performed for other indications [57]. Cysts may be solitary, associated with dysplasia, or associated with polycystic renal disease. Patients with cystic renal disease or with a family history of cystic disease should be referred to a pediatric nephrologist. Bleeding associated with cystic disease may be considerable and may require immediate nephrologic or urologic evaluation.

Hypercalciuria

An association between hematuria and hypercalciuria was first noted in 1981 in children with asymptomatic macroscopic or microscopic hematuria without signs of renal stones [58,59]. These children had increased urinary excretion calcium despite normal serum calcium levels. Some were otherwise asymptomatic, but others eventually developed urolithiasis. Because of this, the

measurement of urinary calcium excretion has become a standard part of the evaluation of hematuria in children.

Many conditions can result in hypercalciuria, including hyperparathyroidism, immobilization, vitamin D intoxication, and idiopathic hypercalciuria. (See later discussion and recent reviews of idiopathic hypercalciuria [60,61].)

Idiopathic hypercalciuria may result from a tubular leak of calcium (*renal hypercalciuria*) or from increased gastrointestinal absorption of calcium (*absorptive hypercalciuria*). The mechanism whereby hypercalciuria causes hematuria is unclear. It has been assumed either that hematuria is the result of irritation of the uroepithelium by microcalculi or that microscopic areas of nephrocalcinosis cause bleeding. Urine erythrocytes are shaped normally and RBC cast are absent. There is often a family history of renal stones, and some authors recommend evaluation of parents and siblings for hypercalciuria. In contrast to benign, idiopathic hematuria, macroscopic bleeding and occasional blood clots may be seen in patients with hypercalciuria. Symptoms may include dysuria, suprapubic pain, or renal colic. The author does not restrict calcium in children because osteopenia may result, and reserves therapy with thiazide diuretics (to enhance calcium reclamation from the glomerular filtrate) for patients with recurrent episodes of macroscopic hematuria or a family history of urolithiasis, or those who develop a stone [62].

Renal transplant

Children with renal transplants are at risk for developing urolithiasis, the only manifestation of which may be hematuria [63]. Review of 21 patients showed that one third had persistent microscopic hematuria. Patients with and without hematuria had similar baseline characteristics. The etiology of hematuria was pre-existing (one patient), recurrent IgA nephropathy (one patient), cytomegalovirus nephritis (one patient), and unexplained (four patients). None had renal calculi or hypercalciuria. Three of the four patients with unexplained hematuria have chronic allograft nephropathy, and the fourth (original disease dysplasia) had hypocomplementemia. Five years after onset of hematuria, all patients are alive with stable allograft function. Causes of posttransplant hematuria, although diverse, are stone disease in less than 2% of patients. Whether chronic allograft nephropathy causes hematuria remains to be determined. Renal biopsies should performed to look for recurrent or de novo glomerulonephritis with onset of hematuria if proteinuria or deterioration of renal function is seen.

Urinary tract and vascular infection

In children the most common cause of hematuria is urinary tract infection. (Please see the article by Shortliffe elsewhere in this issue for further exploration of urinary infection.)

Trauma

Pelvic fractures and abdominal/chest injuries help identify patients who require evaluation of the genitourinary tract. The need for genitourinary tract evaluation in pediatric trauma patients is based as much on clinical judgment as on the presence of hematuria [64]. Children with microscopic hematuria of greater than 50 RBC/hpf or macroscopic hematuria, even in the presence of a benign abdominal examination, should undergo imaging with an abdominal CT scan [18]. Significant renal injuries are unlikely in pediatric patients with blunt renal trauma but no gross or less than 50 RBC/hpf microscopic hematuria [18]. Most children with renal injury are managed conservatively [65]. When blood is present at the urethral meatus, cystourethrography is required to look for urethral or bladder injury [66].

Hemangiomas and polyps

Hemangiomas in the urinary tract may cause hematuria, but these are often impossible to locate and are only clinically significant if there is gross bleeding; therefore, hemangiomas require diagnostic testing and treatment only if they manifest with macroscopic hematuria [67]. The most common presenting symptoms of urinary tract polyps are hematuria and urinary tract obstruction. Transurethral resection is curative [68].

Loin pain hematuria syndrome

Loin pain hematuria syndrome (LPHS) was first reported in 1967 by Little and colleagues [69] and refers to episodes of unilateral or bilateral lumbar pain accompanied by macroscopic or microscopic hematuria. The diagnosis is made by exclusion after patients are shown to have normal renal function, normal genitourinary system, no infection, no malignancy, no hypercalciuria or nephrolithiasis, and no previous trauma. Most patients are women between 20 and 40 years of age, but there are reports of LPHS in children [70,71]. The pathogenesis of LPHS is unresolved; although a vascular cause seems most likely, renal

biopsy is not helpful [72]. The symptoms of LPHS are similar to those found in parents of children with Munchhausen syndrome by proxy (MSBP). MSBP must be excluded in all children where LPHS is considered. Almost 50% of patients with LPHS have psychopathologic disturbances [73,74]. The author agrees with Gusmano [75] in questioning the existence of LPHS, particularly in children.

Idiopathic urethrorrhagia

Urethrorrhagia usually presents in prepubertal boys. Symptoms included urethrorrhagia (terminal uretheral hematuria) and dysuria (33%). Cystourethroscopy reveals bulbar urethral inflammation. Routine radiographic, laboratory, and endoscopic evaluation is unnecessary for evaluating urethrorrhagia. Spontaneous resolution occurs in over 90% of children. Watchful waiting is indicated. In children with prolonged urethrorrhagia, evaluation should be considered because urethral stricture may be identified [76].

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Medical management of pediatric stone disease

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Childhood urolithiasis remains endemic in certain parts of the world, namely, Turkey and the Far East. In these areas, bladder stones composed of ammonium acid urate and uric acid predominate, strongly implicating dietary factors, particularly the dependence on cereal and rice. In the United Kingdom and other European countries, 75% of calculi in children are composed of organic matrix and struvite, and many are found coincident with proteus infection and urinary tract anomalies. In contrast, in the United States and Scandinavia, infectious stones are rare.

The prevalence of nephrolithiasis in North American children varies widely among geographic regions and accounts for 1 per 1000 to 1 per 7600 pediatric hospital admissions, a rate one-tenth of that seen in adults [1]. Stones occur in children of all ages and do not disproportionately affect any age group. In general, there is no gender preference in children with urolithiasis [2,3] aside from a slight male preponderance, which is evident only in children with hypercalciuria and those with genitourinary anomalies [3]. Stones are uncommon in African-American children.

The rate of recurrent stones in childhood has been reported to be 6.5% to 54% with a mean interval to recurrence of 3 to 6 years [2–8]. Children with an identifiable metabolic disorder are nearly fivefold more likely to have recurrent stones than those with no identifiable metabolic disorder [2].

Manifestations

Clinical manifestations of stone disease are often more subtle in children, particularly younger children, when compared with the dramatic adult presentation with incapacitating pain. Abdominal, flank, or pelvic pain occurs as the initial clinical feature in approximately 50% of children with urolithiasis [3,9], whereas gross or microscopic hematuria leads to the diagnosis in 33%, incidental radiographic findings in 15%, and infection in 11% [3]. In infancy, pain from stones may mimic colic. Among children 5 years of age and younger, urinary tract infections and incidental radiographic findings lead to the diagnosis in 43% compared with 15% of the time in children 12 to 16 years of age [3]. Symptoms such as urgency, dysuria, frequency, and fever, as well as pyuria or documented urinary tract infection, are noted in approximately 20% to 50% of patients [1,10,11]. Thirty-seven percent of children with urolithiasis have a positive family history of such [3]. Microscopic or macroscopic hematuria has been reported in 33% to 90% of children with stones. In the United States, three fourths of pediatric stones are renal in location, with 10% being ureteral and 10% located in the bladder [3]. Younger patients are more likely to present with renal versus ureteral calculi. In addition, these stones tend to be larger in younger children; therefore, they have a lower rate of spontaneous passage [2]. The passage rate for ureteral calculi is surprisingly consistent in all age groups, with stones greater than 5 mm rarely passing spontaneously [2].

The popularity of urinary undiversion, bladder augmentation, and continent urinary diversion has contributed to an increased frequency of bladder calculi.

Etiology

As is true in adults, greater than 75% of all urinary tract calculi reported in North American children are composed of calcium oxalate or

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calcium phosphate [3,12]. Infection stones, which represent 15% to 25% of the total, are the second most common form of calculosis [3,5–7]. The published etiology of renal stones in childhood varies depending on the source of the review, namely, a surgical or medical population, but in two large pediatric series that included both patient populations, metabolic conditions were found to account for greater than 50% of diagnoses [3,12]. In a purely surgical series of pediatric stone patients, urinary tract anomalies take on much more relevance [5]. A variety of genitourinary anomalies are found in 30% of children with urolithiasis [3].

Pathophysiology

Urine is a complex solution containing ions that interact with other constituents. The generation of crystals is a process that is variably promoted or inhibited by several physicochemical or anatomic factors. These factors include the solute excretion rate, urinary supersaturation, urinary ionic strength, urinary flow rate, urine pH, and urinary tract developmental anomalies. In normal urine, the concentration of a component necessary to reach supersaturation is several times higher than would be expected from its solubility because of the presence of organic and inorganic inhibitors, that is, magnesium, glycosaminoglycans, glycoproteins, citrate, pyrophosphate, and nephrocalcin [13]. Urine pH affects the saturation of some potential stone-forming solutes by altering their solubility. Acidic urine decreases the solubility of uric acid and cystine, whereas an alkaline pH is conducive to the formation of struvite and calcium-containing stones.

Urinary supersaturation indexes that consider lithogenic and stone inhibitory substances in the urine have been shown in the adult stone-forming population to be useful in predicting the risk of stone recurrence [14]. In children, these indexes are more sensitive predictors of recurrent stone risk [15], although pediatric reference ranges have not yet been established.

Evaluation

The evaluation of a child who presents with urolithiasis is not unlike that performed in an adult and should be directed toward identifying any physicochemical, anatomic, and genetic factors predisposing to urolithiasis. Because 78% of all stones analyzed in children are composed of calcium oxalate or calcium phosphate [3], this finding is of limited assistance in the evaluation. Short of finding a uric acid, cystine, or struvite stone, the search for an etiology consists of blood and urine studies (Box 1), including a 24-hour urine collection (for calcium, oxalate, uric acid, sodium, citrate, creatinine, volume, pH, and a cystine screening) obtained on a routine diet. An abnormal value should be reconfirmed and examined in relationship to sodium excretion. For children who are not toilet trained, the evaluation may be performed by obtaining measurements of creatinine, calcium, uric acid, and oxalate on a random urine (Box 2), preferably 2 to 4 hours following a meal in which milk is ingested, if only one sample is obtainable.

The presence and appearance of crystals on a urinalysis provide clues to the type of stone, although only the finding of cystine crystals is pathognomonic. Measurement of intact PTH may be deferred until the results of serum and urinary calcium values are known. Reduced urinary citrate excretion may suggest the diagnosis of distal renal tubular acidosis. In patients with hypercalciuria, if a medullary sponge kidney is suspected in patients with a positive family history, an intravenous pyelogram (IVP) should be performed.

Radiographic evaluation

Similar to the experience in adults, the search for urolithiasis in children with hypercalciuria is best accomplished by performing a nonenhanced

Box 1. Initial laboratory evaluation of a child with urolithiasis

Serum

Complete blood count; electrolytes, bicarbonate, blood urea nitrogen (BUN); creatinine; calcium; phosphorus; magnesium; alkaline phosphatase; uric acid; intact parathyroid hormone (PTH)

Urine

Urinalysis with pH (metered preferable); urine culture; 24-hour urine for calcium, phosphorus, magnesium, oxalate, sodium, uric acid, citrate, cystine, creatinine, volume

Stone analysis

Box 2. Normal values for urinary solute excretion

Timed urine collections
Calcium: <4 mg/kg/24 hr
Oxalate: <30 mg/m^2/24 hr (<50 mg/1.73 m^2/24 hr)
Uric acid: < 815 mg/1.73 m^2/24 hr
Cystine: <75 mg/g creatinine (<60 mg/1.73 m^2/24 hr)
Citrate: >180 mg/g creatinine, >128 (males) or >300 (females) mg/g creatinine
Magnesium: 1.6 ± 0.8 mg/kg/24 hr

Urinary solute: creatinine ratios[a]
Calcium: children, <0.21; neonates, <0.6–0.81 (<34 weeks gestational age) or <0.15–0.42 (>34 weeks gestational age)
Oxalate[b]: 0–6 months, ≤360 (values represent sample means); 7–24 months, ≤174; 2–4.9 years, ≤101; 5 years, ≤82; 9 years, ≤69; 12 years, ≤50; 14 years, ≤56; 16 years, ≤40
Uric acid[c]: <0.56 mg/dL glomerular filtrate if >2 years

[a] LAll ratios are expressed as mg/dL solute ÷ mg/dL creatinine.
[b] Oxalate values are expressed as millimole of oxalate per mole of creatinine, where oxalate mg/88 = __ millimoles oxalate, and creatinine mg/112,000 = __ moles creatinine.
[c] LCalculated as ($U_{UA} \times S_{CR} \div U_{CR}$), where U_{UA} is urine uric acid, S_{CR} is serum creatinine, and U_{CR} is urine creatinine, all in mg/dL.
Modified from Polinsky MS, Kaiser KA, Baluarte HJ, et al. Renal stones and hypercalciuria. Adv Pediatr 1993;40:353–84; with permission.

helical CT scan, as demonstrated by Nimkin et al [16] in a study of 25 children with documented urolithiasis. CT had by far the highest sensitivity for detecting calculi when compared with renal ultrasound, IVP, or abdominal flat plate imaging. Advantages of noncontrast, thin-section, helical CT over excretory urography include shorter examination times, higher sensitivity and specificity for calculi, no need for intravenous contrast, and a greater potential for making alternative diagnoses [17,18]. Disadvantages include a higher radiation dose using current protocols and a higher cost. Despite the demonstrated advantages of CT scans, in practice, many pediatric nephrologists, because of concerns relating to radiation exposure, will use an abdominal flat plate and ultrasound for routine surveillance in the asymptomatic child (monitoring every 12–18 months), reserving the nonenhanced, thin-cut helical CT for patients who are symptomatic.

A comparison of renal ultrasound/abdominal flat plate (RUS/KUB) with CT has not been performed in pediatrics, and further work is needed to optimize CT imaging parameters while maintaining diagnostic accuracy and minimizing the radiation dose. In a small study of children with suspected renal colic and atypical abdominal pain, nonenhanced helical CT was diagnostic in seven children, although this study was not directly compared with ultrasound and KUB [19].

When a stone is seen on ultrasound or CT but is nonopaque on a plain film, the differential diagnosis includes uric acid, cystine, and xanthine stones.

Hypercalciuria

Hypercalciuria is the most common cause of urolithiasis in children, accounting for up to 34% of all pediatric stones [3]. Normal calcium excretion during childhood has been defined as less than 4 mg/kg per day measured in a 24-hour urine collection with the patient consuming a routine diet [20–22], preferably confirmed with a second sample. In children with documented idiopathic hypercalciuria, it is reasonable to institute a sodium-restricted diet (2–3 g/day) for 2 to 4 weeks and recollect a third 24-hour urine sample [23] owing to the known calciuric effect of dietary sodium. A simple screening test for hypercalciuria can be performed by determining the ratio of urinary calcium to creatinine concentrations in a random specimen. Values greater than 0.2 in a 24-hour urine sample [24,25] are considered elevated. Use of

random urinary collections must be interpreted with caution [25], because the urine calcium to creatinine ratio may increase by 40% to 0.28 following a meal [25]. Neonates and infants have higher calcium excretion and lower creatinine excretion than older children. Sargent et al [26] have reported that the urinary calcium-to-creatinine ratio declines during childhood and may generally be higher than previously reported. Urinary calcium-to-creatinine ratios during the first 6 months of life are up to 0.8 mg/mg and, from age 7 months to 1 year, up to 0.6 mg/mg [26–28]. In infants, normal calcium excretion is markedly influenced by diet. Children receiving breast milk have the highest calcium excretion, whereas children given soy-based formulas produce the lowest calcium excretion [27]. No racial or gender differences in calcium excretion have been found in childhood.

The differential diagnosis of hypercalciuria despite normocalcemia is limited in children, with the majority having idiopathic hypercalciuria. Initial studies of idiopathic hypercalciuria suggested two relatively easily defined and genetically distinct subtypes: renal and absorptive. In patients with renal hypercalciuria, urinary calcium excretion was not primarily influenced by dietary calcium intake, did not normalize with dietary calcium restriction, and was associated with increased serum PTH concentrations. Absorptive hypercalciuria was characterized by an exaggerated calciuresis in response to dietary calcium. When patients with absorptive hypercalciuria restrict dietary calcium, urinary calcium excretion returns to normal. In such patients, serum PTH levels are normal. In children and adults, initial studies suggested that the majority of patients with hypercalciuria and urolithiasis had renal hypercalciuria [25,29]. Subsequently, absorptive hypercalciuria has been found to be the most common metabolic cause of urolithiasis in adults. Although considerable effort was expended initially to differentiate renal versus absorptive hypercalciuria in childhood, use of the oral calcium challenge following a week of dietary calcium restriction is no longer recommended. The results have not been reproducible or diagnostic and offer little additional information beyond that obtained from analyzing calcium excretion before and after dietary calcium restriction in children with documented hypercalciuria, with the exception being children with elevated PTH levels. Aladjem et al [30] convincingly demonstrated the lack of reproducibility of the oral calcium challenge when they retested 30 children aged 3 to 7 years after their original classification. Less than half of the children retained their original classification. The pattern of distribution of the patients during restudy was found to be unpredictable by any parameter studied. A highly significant correlation between urinary calcium and sodium excretion was observed during both studies.

Forty-six percent of children with hypercalciuria have a positive family history of urolithiasis, supporting the impression that idiopathic hypercalciuria is a hereditary trait [31]. Although the genetic basis of hypercalciuria is unknown, idiopathic hypercalciuria seems to follow an autosomal dominant pattern of inheritance and can be diagnosed in approximately 4% of an unselected pediatric population [20,31–34]. The pathogenesis of idiopathic hypercalciuria is a continuum of increased renal calcium excretion, increased gastrointestinal absorption, and, occasionally, increased bone resorption [23]. The latter effect has important clinical implications, because lowering calcium intake may lead to negative calcium balance and osteopenia. Recent studies have suggested significant osteopenia in children with familial hypercalciuria [35], leading to a hypothesis that a defect in bone mineralization may be the proximal cause of hypercalciuria, at least in some children.

In three families with severe absorptive hypercalciuria, a gene defect localized to chromosomal area 1g23-q24 has been identified [36]. The factors responsible for the elevation in calcitriol levels in patients with idiopathic hypercalciuria are poorly understood but may include a urinary phosphate leak as a primary defect. Among children who can be classified as having renal hypercalciuria, 1,25-dihydroxy vitamin D_3 levels are found to be incompletely suppressed following a high-calcium diet. A subset of these children may also experience renal glycosuria, hyperuricosuria, or hypocitraturia. Initial efforts to link familial idiopathic hypercalciuria with the vitamin D receptor gene have been unsuccessful. In children and adults, absorptive and renal forms of hypercalciuria most likely represent a continuum of a single disease.

Dent disease is an X-linked recessive disorder of urolithiasis secondary to a form of Fanconi syndrome with hypercalciuria, low molecular weight proteinuria ($\propto$-microglobulin and retinol-binding protein), nephrolithiasis, and nephrocalcinosis [37]. Glycosuria, aminoaciduria, phosphaturia, microscopic hematuria, and renal failure may also occur. Urinary acidification is normal in 80% of cases. Two other conditions, X-linked

recessive hypercalciuric hypophosphatemic rickets and low molecular weight proteinuria with nephrocalcinosis, have been described with similar phenotypes [38]. These diverse syndromes are all caused by mutations affecting a chloride channel [39–41] linked to the short arm of the X chromosome encoding for the *CLC-5* gene. *CLC-5* mutations have not been identified in individuals with idiopathic familial hypercalciuria. It is not clear how loss of *CLC-5* function leads to hypercalciuria; however, abnormal regulation of PTH and 1,25-dihydroxyvitamin D_3 synthesis seems important.

Children with Bartter's syndrome, a condition sometimes inherited as an autosomal recessive trait in which the primary defect is a failure to reabsorb sodium adequately in the thick ascending limb of Henle's loop, have hypokalemia, hypochloremic metabolic alkalosis, and hypercalciuria. Bartter's syndrome is also believed to be related to abnormalities in the family of genes that encode voltage-gated chloride channels.

Table 1 lists possible inheritance patterns for conditions associated with hypercalciuria. A single genetic abnormality responsible for idiopathic hypercalciuria is unlikely, because there seems to be a continuum in the rates of calcium excretion between normal and hypercalciuric humans [42]. Distal renal tubular acidosis (RTA) is an uncommon cause of normocalcemic hypercalciuria and is encountered in 2% to 3% of children with urolithiasis.

Hematuria without overt urolithiasis may be associated with hypercalciuria, hyperoxaluria, and hyperuricosuria [9,43–46]. The clinical presentation of hypercalciuria without urolithiasis may be painless microhematuria, dysuria, urinary frequency, and painless or painful macroscopic hematuria. In the absence of infection, proteinuria, or calculi, hypercalciuria is found as the cause of macroscopic hematuria in 27% of children [9], although the frequency in African-American children is considerably less, and hypercalciuria is only occasionally reported as a cause of hematuria in Asian children. The risk of urolithiasis in a child with hypercalciuria who has had no previous stones has been variably reported but seems to be approximately 13% to 17% within 3 to 5 years [34,47], with a mean interval of 13.1 months (range, 1 to 41 months).

Table 1
Genetics of hypercalciuria

Disorder	Possible Inheritance
Familial idiopathic hypercalciuria	Autosomal dominant
Distal RTA	Autosomal dominant
Bartter's syndrome	Autosomal recessive
Hypercalciuria/hypomagnesemia	Autosomal recessive
Dent's disease	X-linked recessive
X-linked urolithiasis	
Hypercalciuric rickets	
Hypercalciuria with low molecular weight proteinuria	

Data from Thomas SE, Stapleton FB. Leave no "stone" unturned: understanding the genetic basis of calcium-containing urinary stones in children. Adv Pediatr 2000;47:199–221.

Because the single greatest risk factor for stone formation is a low urinary flow rate, the cornerstone of preventative management is maintenance of adequate daily fluid intake with the resultant production of at least 1400 mL/1.73m^2/day of urine, with an empiric increase of as much as 25% in warm weather [10]. Dietary sodium intake influences urinary calcium excretion in children with and without hypercalciuria [35]. Dietary sodium restriction is recommended as is maintenance of calcium intake consistent with the Recommended Daily Allowance (RDA) for children. In addition, a high-potassium, low-oxalate diet is recommended for children with hypercalciuria and urolithiasis. A low-calcium diet is not effective in reducing the risk of stone recurrence and poses a substantial risk to maintenance of bone health [48,49]. In children who have documented urolithiasis, thiazide diuretics are often used in conjunction with high urinary flow rates and dietary sodium restriction. Some attenuation of the hypocalciuric response to thiazide diuretics has been seen after 3 months use [50], and their prolonged use can lead to hypokalemia with resultant hypocitraturia [51]. Consequently, serum potassium must be monitored at regular intervals, and, when supplementation is required, it should be provided as potassium citrate. In patients with hypercalciuria, consideration should be given to monitoring bone density as a proxy for calcium balance.

Hypercalciuria associated with distal RTA is best treated with sufficient potassium citrate to correct the metabolic acidemia and hypokalemia and to normalize urinary calcium and citrate excretions.

Calcium oxalate stones have occurred in immobilized patients confined to bed for as little as 3 weeks, necessitating maintenance of an adequate

urine flow rate and monitoring of urinary calcium excretion in such a clinical setting.

Uric acid urolithiasis

Uric acid is the end product of purine metabolism. As many as 8% of children with metabolic stones have hyperuricosuria [3]. Hyperuricosuria predisposes not only to uric acid precipitation but also to calcium oxalate lithiasis, the latter by epistaxis. Two major factors promote uric acid precipitation: a high urinary concentration of uric acid and a urinary pH of less than 5.8.

Hyperuricosuria may result from uric acid overproduction, or may occur in the presence of normal serum uric acid levels. The presence of urate stones and elevated serum uric acid may be secondary to inborn errors of metabolism, such as Lesch-Nyhan syndrome (hypoxanthine quanine phosphoribosyltransferase deficiency), type I glycogen storage disease, myeloproliferative disorders, or other causes of cell breakdown. Primary gout owing to partial hypoxanthine guanine phosphoribosyltransferase deficiency with uric acid calculi occasionally occurs in older children. Uric acid stones may also be seen in 5% to 10% of children placed on a ketogenic diet for seizure control [52,53]. Children maintained on a ketogenic diet often have evidence of hypercalciuria, acidic urine, or low urinary citrate excretion, which in conjunction with low fluid intake, places these children at high risk (5% to 10% incidence) for uric acid and calcium stone formation [52]. Hyperuricosuria can also occur secondary to excessive dietary purine/protein intake or uricosuric drugs such as sulfinpyrazone, high-dose aspirin (>2 g/day), ascorbic acid (>4 g/day), phenylbutazone, and probenecid.

Uric acid excretion is extremely high in the neonatal period and remains substantially higher than adult values throughout early childhood. Unfortunately, total urate excretion, excretion per unit body weight, and fractional excretion of uric acid all vary with age; therefore, age-related normal values rather than a single normal value must be used. A normal value of less than 0.56 mg of uric acid per deciliter of glomerular filtrate may be used after 2 years of age. This value may be calculated by the following formula [54]:

$$\frac{\text{Urine uric acid} \times \text{Plasma creatinine}}{\text{Urine creatinine}} = \text{mg/dL GFR}$$

Primary treatment goals are increased fluid intake and urinary alkalinization to a pH of 6.5 to 7.0 with potassium citrate (preferable) or sodium bicarbonate. Reduction of dietary protein to the RDA for height age may be recommended. Use of the xanthine oxidase inhibitor allopurinol is indicated when fluid and urine alkalinization fails to prevent stone recurrence, or when hyperuricosuria is present in excess of 1 g/1.73m^2/day. Patients with myeloproliferative disorders may benefit from decreasing uric acid production with allopurinol. Because hydration and alkalinization can lead to dissolution of uric acid stones, more invasive procedures are often not required. Radiographically, uric acid stones are typically radiolucent.

Struvite stones

Infection-related stones account for 2% to 24% of children with nephrolithiasis [3,5–7,12] and as many as 75% of stones in European children. Infection stones are more common in males and are usually detected before the age of 6 years. More than half of all children with infection-related stones have genitourinary anomalies [3]. Affected children have persistent pyuria, bacteriuria, and struvite crystalluria.

Infection stones consist of an organic matrix of Tamm-Horsfall glycoprotein, struvite (Mg-NH_4-PO_4), and triple phosphate and apatite ($CaPO_4$). Most of the components of struvite stones (calcium, phosphate, magnesium, and urea) are present in adequate concentrations for stone formation in normal urine. Infection by urea-splitting bacteria results in an increased, markedly elevated urinary pH owing to large amounts of NH_4 production and increased urinary magnesium ammonium phosphate, conditions favoring the formation of struvite and carbonite apatite crystallization. The resultant stones, which have a tendency to grow rapidly and form staghorn calculi, are contaminated intrinsically by bacteria. *Proteus* species are isolated from more than 70% of all patients with infected stones, although *Pseudomonas, Klebsiella, Streptococcus, Serratia, Providencia, Staphylococcus, Candida*, and *Mycoplasma* species may also produce urease.

Successful management of infection stones requires the elimination of urinary stones and fragments, the correction of anatomic or functional obstruction, and sterilization of the urine. Eradication of the stones is often difficult given the tendency of struvite crystals toward rapid growth and the formation of staghorn calculi. Long-term suppressive, culture-specific antibiotic therapy

(particularly if there are residual stone fragments) is often necessary. Lavage chemolysis, urease inhibitors, acetohydroxaminic acid (AHA), and urinary acidification are adjunctive therapies to be considered.

Because ureolysis is the primary cause of struvite stones in humans, inhibition of urease retards the growth of existing stones and most likely lessens the risk of new stone formation. There is good clinical and experimental evidence to support the use of urease-inhibiting drugs [55]. Urease inhibitors may have a role in palliation, as opposed to actual treatment, of infection stones. The combination of urease inhibitors and antibiotics is synergistic. The difficulty associated with urease inhibitors is related to their toxicity. The greatest experience is with AHA, which is more potent than the other available urease inhibitor hydroxyurea. As many as 30% of adults are unable to tolerate AHA because of gastrointestinal and neurologic symptoms. Although urinary acidification, in theory, should be beneficial to increase the solubility of struvite and carbonate apatite, long-term studies of successful urinary acidification are lacking.

Cystinuria

Cystinuria accounts for 2% to 7% of children with metabolic urolithiasis in industrialized countries [3, 5]. Cystinuria is an incompletely recessive autosomal disorder characterized by failure of tubular reabsorption of four basic amino acids: cystine, ornithine, lysine, and arginine. It occurs with a frequency of approximately 1 case per 15,000 population in the United States. Only cystine has poor solubility in the normal urinary pH range. The solubility of cystine in urine is about 250 mg/L up to pH 7 but sharply rises with higher pH, up to 500 mg/L or more above pH 7.5. Urinalysis reveals the characteristic flat hexagonal cystine crystals in 26% of patients. A positive nitroprusside test indicates a level of greater than 75 mg/dL of urinary cystine, and this result needs to be confirmed by a 24-hour collection. Because the genetic transport defect exists from birth, stone formation begins in the first decades of life, with 25% of affected patients passing their first stone in childhood. The permanent excretion of excessive amounts of cystine is spontaneously associated with the relentless formation of stones, which can have a staghorn development. Because cystine stones are poorly fragmented by extracorporeal shock wave lithotripsy (ESWL), regular medical treatment is of particular importance in affected patients.

For many years, cystinuria was considered a genetically homogeneous disorder, and the three different phenotypes, which are distinguished by the degree of derangement in intestinal amino acid transport, were thought to be caused by allelism of the same gene. Recent genotypic and phenotypic correlation data, combined with linkage results, have provided strong evidence for the presence of genetic heterogeneity in cystinuria. Type I cystinuria is associated with an amino acid transporter gene on chromosome 2p. More recently, the identification of the cystinuria type III locus on the long arm of chromosome 19 has been reported, and preliminary data suggest that type II families share the same locus. There may be additional unidentified genetic defects. Patients with type I/I cystinuria have the highest risk for nephrolithiasis. Concomitant hypercalciuria, hyperuricuria, and hypocitraturia owing to a renal tubular acidification defect have been reported in adults with cystinuria, predisposing these individuals to calcium and uric acid urolithiasis as well.

The goal of treatment in patients with cystinuria is to obtain solubilization of cystine excreted in the urine. This goal can be accomplished in three ways: (1) dietary measures allowing reduction of cystine production (by decreasing methionine intake), urinary excretion (by low sodium intake), or both; (2) conservative measures directed at decreasing cystine concentration (by hyperdiuresis) with or without increasing its solubility (by alkalinization); and (3) treatment with chelating agents (sulfhydryl compounds) that convert cystine to a more soluble disulfide, reducing excretion of the poorly soluble free cystine.

Treatment goals include maintaining urinary flow rates of 50 mL/kg/day, dietary protein and sodium restriction, and urinary alkalinization with potassium citrate to maintain a urinary pH above 7.5. The daily intake of fluid and alkali should be sufficient to maintain urinary cystine concentration below 300 mg/L. The fluid intake should be distributed throughout the day and night. Fruit juices (citrus or orange) are useful, because they contain citric acid and potassium, increasing diuresis and alkali load. Lowering daily sodium intake to 50 μg can markedly reduce cystine excretion, although the mechanism by which this occurs is incompletely understood. A substantial decrease in cystine excretion on a low-sodium diet has been seen in adults and children [56]. Methionine, an essential amino acid, is the precursor of

cystine. Reduced methionine intake lowers cystine production but cannot be lower than the physiologic requirement, that is, 1200 to1400 mg/day. Most authorities believe that such dietary restriction is not advisable for children. Alkali is best given as potassium citrate. Unlike bicarbonate, citrate interferes with the calcium oxalate crystallization that may result from urinary alkalinization and from the idiopathic hypercalciuria or hypocitraturia that are simultaneously present in some patients.

The chelating agents D-penicillamine and ∝-mercaptopropionyl glycine (Thiola) are also used as adjunctive therapies. Both compounds are sulfhydryls that cleave cystine into two cystine moieties to form a mixed disulfide 50 times more soluble than cystine itself. Half the daily dose of chelating agents should be given at bed time, because cystine concentration in urine is maximal during the night. Side effects have developed in as many as 50% of patients receiving D-penicillamine and include fever, rash, nephrosis, pancytopenia, hypogeusia, and epidermolysis. Side effects with ∝-MPG are seen in 65% to 76% of those treated but are less severe than the effects seen with D-penicillamine.

Conflicting results have been reported regarding the effect of captopril on cystine excretion. Captopril contains sulfhydryl groups leading to the formation of captopril–cystine complexes that are 200 times more soluble than cystine alone (and three to four times more soluble than the disulfides formed with penicillamine and tiopronin). Results in children have been less encouraging [57–59].

Disappearance of cystine crystals in the first-morning urine is an excellent index of treatment efficacy. Cystine stones are radiopaque owing to their sulfur content but are usually not as dense as calcium-containing stones; therefore, they may be missed on abdominal flat plate imaging. Cystine stones are often resistant to ESWL; therefore, percutaneous surgery or ureteroscopy are often preferred methods of stone extraction.

Cystinuria is a different disorder from cystinosis, which is an autosomal recessive disorder of lysosomal cystine transport that results in excessive intracellular accumulation of free cystine, leading to Fanconi syndrome and progressive renal failure but not urolithiasis.

Hyperoxaluria

Oxalate is a product of human metabolism produced in the liver and excreted primarily by the kidney. Oxalate is also absorbed from the diet, and renal excretion reflects the combined endogenous and exogenous oxalate loads. Hyperoxaluria accounts for a small but significant portion of pediatric stone disease.

Primary hyperoxaluria usually presents as calcium oxalate stone formation or nephrocalcinosis during childhood. Some patients never have clinical stone disease; rather, they experience progressive loss of renal function owing to calcium oxalate deposits in the renal interstitium. Approximately 50% of children with primary hyperoxaluria have symptoms by age 5 years. Primary hyperoxaluria is usually diagnosed by the finding of elevated urinary oxalate on a 24-hour urine collection, with hyperoxaluria in children defined as exceeding 1.0 to 1.5 mmole/1.73m^2/24 hours. Oxalate excretion in childhood varies with age, with infants normally excreting four to five times more oxalate than preschool children. Most endogenously produced oxalate is derived from glyoxylate. Any alteration in glyoxylate metabolism that leads to increased hepatocyte glyoxylate levels will lead to increased oxalate production. One of the critical enzymes regulating this process is alanine glyoxylate transferase (AGXT), a hepatic enzyme located specifically in peroxisomes in humans that converts glyoxylate to glycine.

Type 1 primary hyperoxaluria (PH1) accounts for most oxalosis and for approximately 1% of chronic renal failure in childhood. In patients with PH1, there is a reduction or absence of alanine glyoxalate aminotransferase (AGT) activity that leads to increased glyoxylate levels with a resultant increased conversion to oxalate. Multiple mutations of the gene for AGT, located on chromosome 2, have been found to cause PH1. Because AGT is expressed predominantly in the liver, definitive diagnosis of the disease requires liver biopsy to assess AGT catalytic activity and immunoreactivity. Reduced or absent AGT activity leads to excessive build-up and urinary excretion of oxalate and glycolate, with the formation and deposition of insoluble crystals primarily in the urinary tract and renal parenchyma, leading to recurrent urolithiasis, nephrocalcinosis, and, ultimately, renal failure and systemic oxalosis. There is considerable phenotypic, enzymatic, and genetic heterogeneity within PH1, with manifestations of the disease occurring between infancy and the seventh decade. Diagnosis can be suspected in the presence of elevated urinary oxalate and glycolate levels. Increased urinary glycolate occurs in 70% to 75% of patients with PH1. In children with PH1, the

plasma oxalate and plasma CaOx saturation are elevated even with normal renal function. The level of plasma calcium oxalate supersaturation is thought to be the major determining factor leading to calcium oxalate crystal deposition.

In addition to measuring glyoxylate metabolites in the urine and plasma and performing an enzymologic assay on liver tissue, DNA analysis offers an additional tool in the diagnosis of PH1. Mutational analysis of the gene for AGXT has been used in lieu of liver biopsy to confirm the diagnosis [60]. Genetic analysis can also be used in the prenatal diagnosis of PH1; however, owing to the large number of rare mutations, genetic diagnosis requires family linkage analysis.

Primary hyperoxaluria type 2 (PH2) is characterized by a less severely affected phenotype and results from a deficiency of hydroxypyruvate reductase activity and glyoxylate reductase. Both forms of the disease are autosomal recessive. Children with PH2 usually do not present until their second or third decade of life, and the diagnosis is made following documentation of elevated urinary oxalate and L-glycerate levels. The GRHPR gene has been localized to chromosome 9.

PH1 is more common than PH2, although accurate prevalence rates are difficult to obtain, because many early studies did not carefully segregate the two forms of the disease. The Mayo Clinic found that 20% of their patients with primary hyperoxaluria had PH2. In a comparison of the clinical features of PH1 and PH2, Milliner et al [61] found that the average age of onset and age of diagnosis were similar. Urinary oxalate was higher in the PH1 group, but there was considerable overlap between the populations. Although PH2 has a less severe clinical course, rare cases can progress to chronic renal failure.

Finding elevated urine glycolate (PH1) or glycerate levels (PH2) in the presence of severe hyperoxaluria is diagnostic of primary hyperoxaluria. Unfortunately, neither test is 100% sensitive, because approximately 25% to 30% of patients with PH1 documented by liver enzyme analysis have normal urine glycolate levels. Although liver biopsy is the gold standard for diagnosis, it is not clear that every patient suspected of having primary hyperoxaluria needs a liver biopsy. Therapy to prevent stones will not be altered by classifying the type of primary hyperoxaluria. The decision to pursue a liver biopsy is based on the risk versus benefit of a liver biopsy, patient interest in a definitive diagnosis, and the availability of facilities to analyze the liver biopsy properly. Certainly, if a liver transplant is considered as therapy, a definitive diagnosis is required [62].

Glycolate oxidase, another hepatic enzyme contributing to glyoxylate synthesis, a key precursor step of endogenous oxalate, is a candidate for a third form of inherited hyperoxaluria.

Therapy for primary hyperoxaluria is directed at reducing oxalate excretion or increasing the solubility of calcium oxalate in urine. High water intake is a cornerstone of therapy. To avoid exacerbating hyperoxaluria, patients should be instructed to avoid high-oxalate foods, although most excreted oxalate is endogenously produced. The only pharmacologic intervention known to reduce urinary oxalate in primary hyperoxaluria is pyridoxine supplementation. Pyridoxine is a cofactor for AGT-mediated conversion of glyoxylate to glycine. Approximately 25% to 30% of PH1 patients can lower urinary oxalate excretion significantly with the administration of pyridoxine. Patients with residual AGT function on liver biopsy tend to be more likely to have a response to pyridoxine. Pyridoxine is not effective in PH2 but should be given in a trial to all patients with PH1 and any patient in whom classification of primary hyperoxaluria is not clear.

Neutral orthophosphate in combination with pyridoxine has been used as long-term therapy at the Mayo Clinic for the treatment of primary hyperoxaluria [63]. Orthophosphate reduces calcium oxalate crystallization by (1) reducing intestinal calcium absorption by suppressing calcitriol production, which leads to lowered calcium excretion; (2) increasing excretion of pyrophosphate, an inhibitor of calcium crystallization; and (3) reducing calcium oxalate supersaturation by providing more phosphate in the urine to complex calcium. The combination of orthophosphate and pyridoxine is the best-documented long-term therapy for primary hyperoxaluria.

Potassium citrate complexes urine calcium and is a direct inhibitor of calcium oxalate crystallization. Citrate has been shown in children with primary hyperoxaluria to decrease urinary calcium oxalate supersaturation rates and to reduce the frequency of stone events [64]. Magnesium oxide, which forms a soluble complex with oxalate in urine, has also been shown to reduce stone formation rate.

The definitive therapy for PH1 is liver transplantation, although the timing of transplant and the selection of appropriate subjects remain

controversial [65]. Because PH2 has an overall better prognosis than PH1, there is no role for a pre-emptive transplant in PH2.

Hyperoxaluria can be caused by defects in oxalate metabolism, overabsorption of dietary oxalate secondary to bowel disease, or consumption of diets rich in oxalate or oxalate precursors. Secondary hyperoxaluria accounts for 50% of stones in children owing to hyperoxaluria and is the result of conditions not dissimilar to those seen in adults. Enteric hyperoxaluria is caused by intestinal (mostly colonic) hyperabsorption, most frequently seen in Crohn's disease or a state in which disease or resection of the small bowel leads to malabsorption of fat and bile acids. In the setting of malabsorption and steatorrhea, dietary calcium is bound by the free fatty acids in the intestinal lumen. Less calcium is available to bind oxalate, resulting in increased amounts of free oxalate for absorption. Patients with inflammatory bowel disease and malabsorption who have had their colon resected do not have significant elevations of urine oxalate. In addition to enteric hyperoxaluria causing calcium oxalate stone disease, as is true in primary hyperoxaluria, the urinary oxalate excretion can be high enough to cause renal damage and renal insufficiency.

Enteric hyperoxaluria is typically evident based on the clinical history or the finding of intestinal malabsorption and varies widely with dietary changes. Other secondary forms of hyperoxaluria include dietary oxalate excess and increased gastrointestinal absorption not owing to gastrointestinal disease or resection. Recent evidence suggests a role for the oxalate-degrading gut flora *Oxalobacter formigenes*, an anaerobic bacteria that colonizes the colon, in the latter form of hyperoxaluria. Intestinal absorption of oxalate ranges between 5% to 15% of dietary intake and is dependent on the amount of free oxalate present in the intestinal lumen. A decrease in the amount of oxalate available for absorption within the colonic lumen as a result of the oxalate-degrading ability of these bacteria is postulated to account for the observed reduction. Significant overlap of oxalate excretion rates between colonized and noncolonized subjects suggests that *O. formigenes* colonization status is just one of many factors determining oxalate excretion [66]. The role of probiotics in the treatment of stone disease is still under investigation, but early studies are promising. A recent study of six adult hyperoxaluric stone formers treated with lactobacillus for 4 weeks showed a reduction of oxalate excretion of 40%.

Box 3. Selected causes of clinical disorders associated with urolithiasis

Calcium lithiasis
Hypercalciuria
- Normocalcemic hypercalciuria
- Idiopathic hypercalciuria
- Absorptive
- Renal
- Distal RTA
- Diuretic-induced (furosemide)
- Secondary to diet: sodium, calcium, vitamin D
- Bartter's syndrome
- "Chloride shunt" syndrome
- Juvenile rheumatoid arthritis

Hypercalcemic hypercalciuria
- Associated with calcium resorption from bone
- Immobilization
- Primary hyperparathyroidism
- Hyperthyroidism
- Adrenocorticosteroid excess
- Adrenal insufficiency
- Osteolytic metastases
- Associated with gastrointestinal hyperabsorption
- Vitamin D intoxication
- Idiopathic hypercalcemia of infancy
- Sarcoidosis

Hyperoxaluria
- Primary hyperoxaluria types 1 and 2
- Enteric hyperoxaluria

Hyperuricosuria

Hypocitraturia
- Metabolic acidosis/distal RTA
- Thiazide diuretics
- Hypokalemia

Uric acid lithiasis
Familial

Chronic volume depletion
- Ketogenic diet

Overproduction of uric acid
- Increased purine biosynthesis
- Lymphoproliferative and myeloproliferative disorders
- Polycythemia
- Inborn errors of metabolism
- Hypoxanthine guanine phosphoribosyltransferase deficiency
  - Complete: Lesch-Nyhan syndrome

Partial: gout
Type I glycogen-storage disease
Hyperuricosuria
High purine intake
Uricosuric drugs

Struvite lithiasis
Inborn errors of metabolism associated with lithiasis
Cystinuria
Hereditary xanthinuria
Adenine phosphoribosyltransferase deficiency
Orotic aciduria
Developmental anomalies of the urinary tract

Treatment of diet-dependent hyperoxaluria consists of restriction of high-oxalate foods and maintenance of a normal calcium intake to limit intestinal oxalate absorption and, possibly, avoidance of excessive protein consumption. Foods rich in oxalate, in order of decreasing content, include rhubarb, spinach, soy burgers, beetroot, almond, tofu, pecans, peanuts, okra, chocolate, collard greens, and sweet potatoes. Dietary calcium and protein intake are important factors determining urine oxalate excretion and stone formation in adults. Dietary calcium restriction has been shown to increase the stone formation rate in patients with idiopathic hypercalciuria owing to increased urinary oxalate excretion [67]. Use of calcium and magnesium supplements with meals increases intestinal binding of oxalate and reduces absorption. Cholestyramine can be added to bind bile acids, which may reverse the increased permeability in the colon and, in addition, bind oxalate.

The role of ascorbic acid supplements, which can be broken down to oxalate, as a cause of hyperoxaluria remains controversial and is complicated by technical problems encountered in the measuring of oxalate in the presence of ascorbate. Although high-dose vitamin C has been associated with extreme hyperoxaluria, the role of ascorbic acid seems to be minimal in routine kidney stone disease in adults.

Traditionally, urinary oxalate excretion has been considered to be abnormal if greater than 50 mg/1.73 m^2/day. This value is clearly inappropriate for infants, in whom urinary oxalate excretion may be four to fivefold greater than in preschool children [68]. Oxalate excretion is higher in formula-fed infants than in those fed human milk.

Hypocitraturia

A decrease in the excretion of urinary inhibitors of crystal formation can promote the development of stones. A principal inhibitor of stone formation is citrate. Hypocitraturia can occur in isolation or in association with hypercalciuria, hyperuricosuria, or hyperoxaluria. Citrate excretion can be limited by chronic metabolic acidosis, induced by chronic diarrhea, RTA, or a high-protein diet, as well as hypokalemia.

Clinical disorders associated with urolithiasis in children are listed in Box 3 [10].

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Surgical management of children with urolithiasis

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The management of urolithiasis in children and adults is similar owing to advances in endoscopic equipment that allow access to the entire ureter and kidney, such that the need for open surgical removal of stones is rarely encountered. Nevertheless, children pose specific technical challenges that require planning before endoscopy and that affect the risks and outcomes of these procedures. The indications for operative intervention in children are similar to those in adults: infection, persistent symptoms of flank pain, nausea, and vomiting, as well as the failure to pass a ureteral stone after an appropriate trial of observation (3–6 weeks). Specific adjustments for performing extracorporeal shock wave lithotripsy (ESWL), ureteroscopy, percutaneous nephrolithotomy, and cystolithotomy in children are discussed.

Diagnosis and follow-up

Renal calculi in neonates and younger children are often diagnosed using ultrasound, and the size of the stone is accurately measured. Ureteral calculi can be seen at the ureteropelvic junction or in the intramural ureter of the bladder. Hydroureteronephrosis may suggest the presence of a stone, but the lack of dilation does not mean that a stone is not present. Repositioning the patient may help determine whether an echogenic focus with posterior shadowing is a single stone or several smaller stones. Older children and teenagers who present with flank pain are usually evaluated with noncontrast spiral CT scanning, as in adults. The abdominal plain film is helpful in this setting to determine whether the stone can be treated by fluoroscopic-controlled ESWL, and whether the stone can be followed up by obtaining plain films during the period of expectant management. If a stone is found following a contrast CT obtained for suspected appendicitis, a delayed plain film will help in showing columnation of contrast to the level of the stone. Intravenous pyelography (IVP) is less often used to make the diagnosis of a stone but may be helpful in follow-up when it is important to delineate the ureteral anatomy. After treatment, the stone-free status may be defined using a plain abdominal film, renal ultrasound, or CT scan. Controversy exists regarding which of these modalities should be used to define the stone-free state, because they have differing sensitivities [1]. After the patient becomes stone free, ultrasound screening is performed at 3- to 6-month intervals, depending on the underlying disease process. If there are residual fragments, retreatment will depend on their size, location in the urinary tract, and likelihood of obstruction, and the growth of fragments over time. Follow-up is individualized and based on age, anatomy, stone burden, and any underlying metabolic abnormality.

Antibiotic use

If the urine is sterile at the time of diagnosis and there is partial obstruction, the use of antibiotics is optional. Antibiotics are generally indicated in patients with high-grade obstruction and in patients who have an indwelling ureteral stent. Similar to the experience in adults, antibiotics are not necessary for ESWL if the urine is sterile, although there is evidence of higher infection rates after ESWL in patients who do not receive

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antibiotic prophylaxis [2]. Every effort should be made to sterilize the urine before ESWL, ureteroscopy, or percutaneous nephrolithotomy.

Equipment

ESWL can be performed using any lithotriptor, but experience with the Dornier HM3 (Dornier MedTech America, Kennesaw, Georgia) and second- and third-generation lithotriptors suggests that, similar to the adult experience, stone-free rates are higher with use of the HM3 [3]. The gantry can be modified to fit the pediatric patient [4]. For patients less than 120 cm tall, the HM3 requires an additional Styrofoam sheet to protect the lungs, which, in children, have a relatively larger excursion than in adults. A benefit of the second- or third-generation lithotriptor in children is that, because the energy is less focused and less intense, there is less risk for pulmonary trauma. ESWL can be performed in children without general anesthesia, although there is probably no advantage of avoiding general anesthesia in a healthy child. Movement makes it difficult to focus the shock waves on the stone, and cooperation is of utmost importance in the sedated or awake patient. Children pass stone fragments well, and the need for a stent for stone passage is rare. If the stone burden is large enough that stenting is considered, alternative procedures such as percutaneous nephrolithotomy should be discussed.

Ureteroscopy requires the smallest available instruments, such as a flexible 6.9F or 7.2F ureteroscope with a 2F and 3.5F working channel, or the semirigid ureteroscopes, which come in 6.9F or 9.4F. The larger semirigid ureteroscopes have a 2F and 5.4 F working channel, whereas the smaller scopes tend to have a single channel for irrigation and instrumentation. The most obvious difference when working with the smaller scopes is the slower rate of irrigation, which is further compromised by guidewire or instrument placement. This rate can be increased by using a pressure irrigation system, although the fluid instilled under pressure still needs some way to drain. Saline should be used in all situations that do not require cautery, owing to the possibility of absorption. A warming system for the irrigation (such as a blood warmer) is important for smaller children and infants who can become rapidly hypothermic during endoscopic procedures.

An assortment of Teflon-coated, hydrophilic, and stiff guidewires is needed in 0.035, 0.028, and 0.018 sizes for the smaller ureteroscopes and stents. With the wide availability of 3F baskets and graspers for stone extraction, manipulation of stones through small endoscopes is identical to that in adults. Tipless baskets are designed for use in the kidney but are useful for stones in other areas of the urinary tract as well. The availability of 3.7F ureteral stents is helpful in younger children. Once patients are in their teens, the ureter will usually accept a 5F or 6F stent. Repeated access to the ureter may helped by placement of an 8 to10F ureteroscope sheath during cystoscopy, although these sheaths may be associated with ureteral trauma or ischemia in children. The authors have tended to use passive dilation via placement of a ureteral stent in preference to balloon or sheath dilation of the distal ureter.

Percutaneous nephrolithotomy requires an access system and appropriate nephroscopes. The "mini-perc," originally modified from a vascular access sheath, allows excellent renal access with a defect of only 11F [5]. Offset all-in-one cystoscopes of approximately 7 and 9F have excellent characteristics for percutaneous work, with working channels of 5F or greater. The flexible ureteroscopes can double as nephroscopes to reach all of the calices of the kidney.

Energy sources for stone fragmentation must be available. Electrohydraulic lithotripsy (EHL) and ultrasonic lithotripsy are widely available and reasonably affordable. The EHL must be deployed carefully in the ureter and should be used with saline, which is as effective as water and safer in the event of absorption [6]. The ultrasonic lithotriptor is beneficial in removing stone fragments as they are produced, but the long probe can make it difficult to use in children. The holmium: yttrium-aluminum-garnet laser is effective in terms of stone fragmentation, and the small 200 μm size of the fiber allows better irrigation during stone manipulation and improved deflection of flexible scopes. Other energy sources, such as the Swiss lithoclast, have been used less frequently in children.

Stone size

It has long been appreciated that children can pass relatively large stones. Younger patients are more likely to have renal than ureteral stones. Renal stones less than 3 mm are likely to pass, and the chance of passing a ureteral stone less than 5 mm in diameter is about 70% [7]. When stone-free rates after ESWL were compared in a group of children and adults who had stones that were matched for size, the children cleared a slightly

greater proportion of stone fragments than adults (95% versus 79%, $P = 0.09$) and seemed to clear them at a faster rate [8].

Results of extracorporeal shock wave lithotripsy

Stone-free rates after one session of ESWL are in the mid-80% range [9–15]. The main concern with the use of ESWL in pediatric kidneys has been the long-term risk of hypertension, loss of renal function, and hyperfiltration. Short-term follow-up to date has failed to show differences in body growth or renal function (glomerular filtration rate determination or dimercaptosuccinic acid/pentetic acid scan) using first-, second-, and third-generation lithotriptors [10,12,14,16]. No increase in blood pressure was noted up to 46 months after ESWL [17,18]. One study found that patients with abnormally small kidneys had fallen further off the growth curve after ESWL, although no difference in overall renal length was found [19]. As is true for adults, the minimum number of shocks at the lowest kilovolt to achieve fragmentation of the stone should be used in children. For the HM3, this is probably 2000 shocks and 17 kV, but evidence that higher levels are clearly harmful is scant [20]. Blood pressure should be checked annually in all children who have undergone ESWL. Because of its high success rates and low morbidity, ESWL is generally considered to be the first-line therapy for stone burden in the kidney under 2 cm and for proximal ureteral calculi that can be visualized easily for targeting.

Technique and results using ureteroscopy

Ureteroscopy is generally indicated for ureteral calculi below the iliac crests, which can be difficult to target with ESWL in children. Ureteroscopy also can be used for upper ureteral and renal calculi, especially after ESWL failure. In smaller children, a period of prestenting with a 3.7F or 5F ureteral stent for 1 to 2 weeks will dilate the ureter sufficiently to allow passage of the flexible or semirigid ureteroscope. Access is gained by passage of a 0.035 guidewire, followed by the placement of a dual-lumen catheter or 8 to 10F dilator/sheath system. An additional 0.035 guidewire is placed in the ureter as a safety wire, and the dual-lumen catheter or 10F sheath is then removed. A 10 to 12F ureteroscope sheath may be placed in the distal ureter if multiple passes of the ureteroscope are anticipated during the procedure, although the authors' preference is to avoid ureteral sheaths in most instances because of the higher risk of ureteral injury in children. The safety wire is sewn to the drapes, labium, or glans. The ureteroscope can then be advanced over the guidewire, or between the guidewires to the stone. Once the stone is visualized, it can be engaged with a basket if it is small. The authors generally prefer fragmentation to avoid the possibility of ureteral avulsion. EHL and the laser are the most commonly used modalities, and the stone should only be pulsed under direct vision to avoid ureteral perforation.

If minimal manipulation is required to remove the stone, no stent is necessary. If the procedure is more complicated, or if there is any question of ureteral injury, a ureteral stent should be left in place for a variable time until the postoperative edema resolves. If injury to the ureter is suspected, the stent should be left for 1 to 2 weeks. Follow-up with ultrasound within a month is recommended to check for hydronephrosis. Vesicoureteral reflux may occur after ureteral dilation but does not seem to cause clinical problems; therefore, routine voiding cystography is not considered necessary [21,22]. Overall, ureteroscopy for ureteral calculi is associated with a 90% stone-free rate with a single procedure [15,21–29].

Technique and results of percutaneous nephrolithotomy

Percutaneous nephrolithotomy is the procedure of choice for a renal stone burden greater than 2 cm, for stones associated with ureteropelvic junction obstruction if endopyelotomy is considered, and for anatomic situations that make stone fragment passage less likely (reconstructed exstrophy, long reimplants). Access can be gained by interventional radiology or in the operating room. Some data suggest that transfusion rates are lower if access is placed preoperatively, and the accuracy of placement may be greater in the radiology suite given the improved fluoroscopic capabilities. If access is gained in the operating room, it is useful to place a ureteral catheter and Foley catheter before positioning the patient prone so that contrast or air may be injected into the collecting system.

Using C-arm fluoroscopy or ultrasound, the appropriate calyx is visualized and entered using a 22G finder needle, or directly with a 16G Chiba needle. The use of air as contrast identifies the posterior calyx preferentially, because air rises posteriorly in the prone position. One can also

aim for a caliceal stone if access to that calyx is preferred. The stylet is removed, and urine flow is confirmed. Contrast can be injected through the needle to confirm placement, but if there is extravasation, the ability to visualize the collecting system may be compromised. A 0.035 guidewire is placed into the collecting system and down the ureter if possible; the skin and fascia are incised; a 10F dual-lumen catheter is placed into the collecting system; and a second 0.035 stiff guidewire is placed. Dilation using balloon or coaxial dilators can then be performed. The mini-perc set (Cook, Spencer, Indiana) uses a modified 11F Cordis introducer that serves as an access sheath [5]; no further dilation is necessary. Although pediatric percutaneous nephrolithotomy was initially performed with 24 to 30F nephroscopes, the mini-perc allows use of 7 to 9.5F rigid cystoscopes and 6.9 to 9F flexible ureteroscopes. It is vital to ensure adequate space within the sheath to allow free egress of irrigating fluid. Warmed saline should be used as the irrigation fluid in children to prevent complications of extravasation or hypothermia [30]. Techniques for stone fragmentation are similar to those used in ureteroscopy, although the ultrasonic device is more universally adaptable through a rigid nephroscope.

After a mini-perc procedure is completed, a 6F nephroureteral stent is left in place for drainage, unless the procedure was for a small stone and required minimal manipulation. Larger sheaths generally require placement of a Foley catheter by cutting the tip off and threading it over a ureteral catheter left through the nephrostomy tract. Stone-free rates approaching 90% can be achieved with a single session of percutaneous nephrolithotomy [5,15,27,31–33].

Cystolithotomy

Patients who perform clean intermittent catheterization can form stones in the bladder owing to the introduction of hair, chronic bacteriuria, or mucus from a bladder augmentation. The surgical approach is complicated by augmentation cystoplasty, bladder neck reconstruction or division, or construction of a continent catheterizable stoma. The lack of an easy access route, such as the native urethra, and the ability to use larger endoscopes and instruments makes a percutaneous approach optimal. If this possibility had been planned for, the patient may have been told at the time of reconstruction of a "safe area" on the abdominal wall through which a needle could be placed should it prove impossible to catheterize per the urethra or via the stoma.

The location for a percutaneous approach can be determined at the time of the procedure by endoscopy of the augmented bladder. After the initial access is obtained with a needle under direct vision from within, dilation can be performed in the manner described for percutaneous nephrolithotomy. Coaxial dilators (Amplatz; Cook Urological, Spencer, Indiana) are generally more useful than balloon dilators because of the abdominal wall scar tissue. It is sometimes possible to first trap the stone in a basket using the flexible cystoscope or ureteroscope passed through the continent stoma, which makes the task of finding the stone in a capacious nonspherical bladder much easier. Ideally, the stone should be removed intact, although there is no evidence that fragmentation of the stone will lead to higher rates of stone formation in the future [34]. The opening in the augment or bladder can be closed primarily or, if it is sufficiently small, allowed to close while the bladder is drained for several days [34,35].

Percutaneous cystolithotomy can generally be performed as an outpatient procedure. A "mini-lap" approach can also be taken by making a small incision in the augment and placing a sheath into the bladder to examine and remove the stones [36]. The patient with an intestinal augmentation should be instructed to irrigate the bladder daily with saline or water to remove mucus, which serves as a nidus for stone formation.

Cystic fibrosis

Patients with cystic fibrosis are at higher risk for renal stone formation. The etiology of the stones has been attributed to hypocitraturia and the lack of oxalobacter formigenes, the latter possibly owing to recurrent antibiotic treatments for pneumonia [37,38]. These patients can be managed with any of the usual methods for urolithiasis. The only unusual perioperative issues are related to pulmonary function; therefore, it is wise to maximize pulmonary function tests before subjecting patients to an anesthetic.

Chemotherapy

Patients undergoing chemotherapy are at risk for uric acid stone formation owing to cell lysis. They are usually given allopurinol once their level of serum uric acid begins to rise. Patients with

symptomatic urolithiasis during treatment can be managed with ureteral stenting and alkalinization of the urine. Percutaneous procedures should only be undertaken in rare circumstances, because the myelosuppression caused by the chemotherapy puts the patient at higher risk for sepsis, and the risk of bleeding is higher owing to the low platelet count.

Ureteropelvic junction obstruction

Children can present with urolithiasis and ureteropelvic junction obstruction. The difficulty in treatment is deciding whether the stone arose owing to the ureteropelvic junction obstruction, or whether the ureteropelvic junction is edematous owing to impaction of the stone. The situation is best assessed antegrade at the time of percutaneous nephrolithotomy. If there is convincing evidence of a high insertion of the ureter, one can incise the ureteropelvic junction posteriorly and leave a nephroureteral stent. Alternatively, one can perform an open or laparoscopic nephrolithotomy and pyeloplasty.

Complications

Because the techniques used in adults and children are the same, the complications are the same. Gross hematuria and bruising of the flank are expected after ESWL. Perinephric hematoma is less commonly encountered, and transfusion is rare. The rate of ureteral injury from ureteroscopy should be approximately 5% and is generally managed by stenting, except in the case of avulsion, which may require open repair, transureteroureterostomy, or ureteral replacement. Bleeding during percutaneous nephrolithotomy is rare in children, but a blood specimen should be available to type and screen if it becomes necessary to transfuse the patient. Infection after stone manipulation results from the release of bacteria from the stone and is managed with intravenous fluids and appropriate antibiotics. Rarely, endotoxins released at the time of stone fragmentation can result in fulminant sepsis; therefore, preoperative antibiotic therapy should be aggressive in patients known to harbor infection stones [39].

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Laparoscopic and robotic approach to genitourinary anomalies in children

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Laparoscopy in pediatric urology is becoming used widely and promises to offer significant benefits to patients, as well as pose novel challenges in the way technology is used. Laparoscopy is a tool, not a specialty. It should be viewed as an adjunct to patient care. The utility of laparoscopy remains to be defined, and will evolve with technology and experience. New technologies such as robotics will impact that evolution further.

How one assesses these technologies will determine the pace and direction of evolution. Unbridled enthusiasm may permit inappropriate care, potentially with negative backlash, and subsequently provoke a technological "ostrich syndrome." Excessive expectations too early in the natural development can impede successful development as a result of unfulfilled expectation [1], and promising new technologies may be lost in the dustbin of history. As with raising a child, unreasonable expectations can have permanent damaging effects. It will be clinicians' responsibility to determine what expectations are reasonable and help guide development of this aspect of pediatric urology. This article reviews the current applications and future horizons of laparoscopy in pediatric urology to provide a broad view of this technology.

Diagnosis

Initial applications of laparoscopy were diagnostic, a use that continues readily on a large scale. The interpretation of the findings have been refined and integrated with operative laparoscopic procedures.

Cryptorchidism

The most widely used laparoscopic application, diagnostic laparoscopy for the undescended testis, aims to provide information as to the presence and location of the nonpalpable testis. Numerous studies have shown it to be safe and accurate—probably more accurate than open exploration [2–4]. There is controversy as to whether it offers an advantage over initial open exploration; two studies have attempted to assess this (one unpublished), with inconclusive results [5]. The underlying concept of diagnostic laparoscopy for the undescended testis is that knowing where a nonpalpable testis is would be a reasonable way to start any operation in search of that testis. The low morbidity of diagnostic laparoscopy tips the balance strongly in favor of initial laparoscopy.

The author's technique is to use a 2-mm scope for diagnosis, placed through a Veress needle containing the sheath for the endoscope, obviating a second blind puncture, which is the major risk for inadvertent injury to an intra-abdominal structure. With diagnostic laparoscopy, one can determine either that a testis is present, in which case appropriate surgical management can be anticipated, or that a testis is absent and no further intervention is needed (unless a prosthesis is to be placed through a scrotal incision).

The presence of an intra-abdominal testis would lead to planning for operative laparoscopic orchiopexy, the most obvious integration of

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diagnostic and operative laparoscopy (Fig. 1). A testis may not be visible in the abdomen and the vas and spermatic vessels are seen passing through the internal ring. This finding suggests either an occult inguinal testis or a vanishing testis in the canal. It should always prompt an inguinal exploration, usually at the level of the pubic tubercle. There is some controversy about the need for this, but the author has seen reasonably viable testes, including a few ectopic testes that were nearly normal, that could not be differentiated clearly from a vanishing testis [6].

Intersex conditions

Although an uncommon indication for laparoscopy, diagnostic and therapeutic laparoscopy has a significant role in the child with an intersex condition [7]. In any case where visualizing the gonad and Müllerian/Wolffian structures beyond what is possible with imaging is desirable, diagnostic laparoscopy can be invaluable. Streak gonads, uterine abnormalities, and inappropriate persistence of Müllerian structures are recognized readily laparoscopically.

Hernia

Laparoscopic assessment of the contralateral inguinal ring at the time of inguinal hernia repair has been described well with large series demonstrating its utility [8]. Controversy remains regarding the interpretation of the observations and risk one may avert by performing a contralateral repair if a patent processes vaginalis is noted [9]. The statistics as to the incidence of subsequent contralateral clinical hernia following unilateral repair can be interpreted in various ways. To some parents, a small risk for a subsequent surgical intervention is enough to warrant the preventive repair, whereas to others it may not be. The level of possible occurrence at some time that would prompt intervention is always arbitrary, and the precision of the number is not relevant. If the surgeon is not to be worried about that risk, then there is little reason to perform a diagnostic laparoscopy.

The author's practice has been to perform contralateral examination with a 70° endoscope (5 mm) passed through the hernia sac using 8 mm Hg insufflation and contralateral visual inspection and palpation. If a patency is present visually or by feeling crepitance (Fig. 2), open exploration is performed. The incidence of contralateral patency seems to increase up to 4 years of age, then to decrease. The author has seen a few young children with normal internal inguinal rings who later presented with a clinically evident hernia, confirmed at repair. This suggests development of the hernia, and parents should be cautioned about this remote possibility.

Extirpative surgery

Nephrectomy

Simple nephrectomy was the first major laparoscopic procedure performed in children and is now well established [10]. The indications are similar to open nephrectomy, which is an uncommon

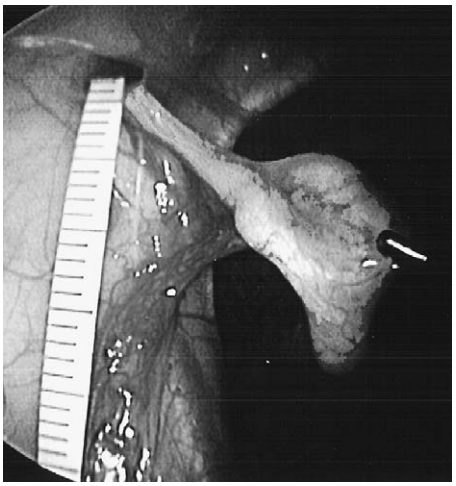

Fig. 1. Intra-abdominal testis on the right viewed laparoscopically.

Fig. 2. Laparoscopic view of patent processus vaginalis in child with unilateral clinical hernia.

operation. Initial experience was transperitoneal with good outcomes. The first cases were performed in infants using three 10-mm cannulae (some used four ports), and no major complications were reported. Patients were discharged the next morning in most cases. An interesting response emerged from a clinical series in which open nephrectomy for multicystic dysplastic kidney through a dorsal lumbar incision was performed and the patients were sent home that day [11]. One can remove a dysplastic kidney through a small incision, although clearly this was a compromised exposure because one case of an inadvertent appendectomy was reported.

Retroperitoneal access emerged in children with excellent results and with much smaller instruments [12–16]. Two access strategies were used: lateral and prone (Fig. 3) [17]. Both work well and have subtle advantages in some cases. The fundamental principles of the procedure are identical, in which the retroperitoneal space is developed using either a balloon or blunt dissection under vision. Two secondary ports are placed and the kidney exposed. In general, the hilum is exposed and controlled first, with subsequent mobilization of the kidney, moving from inferior to superior. Occasionally it is helpful to use the transected ureter as a handle to mobilize the kidney and expose the hilum. Control of the vessels is usually with endoscopic clips (5 mm) or, if small, by cautery (not preferred by the author). The kidney typically is removed through the larger port site (also used for the clip applier). Most of the kidneys were not large enough to require use of a catch-bag or morcellation, although occasionally they would need to be cut into smaller pieces for removal.

The choice of transperitoneal or retroperitoneal nephrectomy largely depends on experience of the operator and associated procedures needed. If the entire ureter needs to be removed, or if an intra-abdominal testis is present, transperitoneal nephrectomy may be best, whereas subtotal resection of the ureter readily permits retroperitoneal access. The prone approach is less suited to ureteral resection, but may be more efficient for access to the hilum.

The relative merits of laparoscopic nephrectomy are debatable. In infants, recovery from open or laparoscopic procedures is rapid. In older children, the difference in postoperative recovery becomes progressively greater. The author's view is to offer the choice to parents, but by learning to perform nephrectomy with equivalent outcomes in infants, one can better offer the advantages of laparoscopic nephrectomy (as well as other more complex procedures) to all children.

Partial nephrectomy

The most useful laparoscopic procedure that emerged from simple nephrectomy is partial nephrectomy for duplication anomalies [18,19]. This is an open operation that probably is done best through a flank incision, which has an appreciable morbidity, even in infants. Precise vascular control is essential, as well as accurate visualization of the normal and abnormal renal moieties. Injury to the remnant pole is the most significant complication, and in the infant undergoing open partial nephrectomy this is more likely with the mobilization required to access the hilum. From a laparoscopic approach, the hilum can be exposed without significant mobilization of

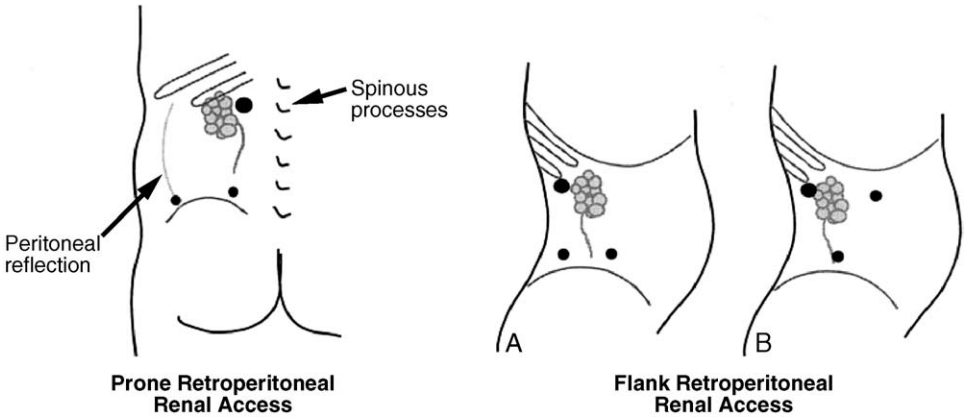

Fig. 3. Port placement for prone retroperitoneal nephrectomy compared with that for the lateral approach.

the remnant pole, theoretically reducing the risk for vascular spasm and injury to the remnant pole. The incidence of this is low enough that it will be difficult to prove a benefit [20].

The author's preferred access to the kidney is retroperitoneal and usually prone [21]. This access limits the ability to remove the ureter, which is needed in unusual cases of reflux with obstruction. In such cases, the lateral approach is used, or a small inguinal counter incision is used to remove the ureter to the level of the bladder neck. If there is simple reflux with no obstruction (usually a lower pole), total removal of the distal ureteral stump is not considered essential, and most data support this contention. Such total removal is an individual decision.

The prone approach provides excellent exposure of the posterior aspect of the kidney and the delineation between the poles is usually evident. The affected ureter is identified at the level of the lower pole, separated from the remnant ureter, which is protected carefully. The affected ureter is transected and used as a handle for mobilization into the hilum. The hilar vessels and the affected pole's vessels are identified. Usually this is accomplished readily, but the vessels may not be apparent. In that case, dissection of the pole is started and the vessels usually become evident with this mobilization. The poles can be separated using either cautery or the harmonic scalpel. If the affected collecting system is entered there is no problem, but any residual collecting system needs to be removed or ablated with cautery. If the remnant pole collecting system is entered, it will need to be repaired and drained. Some have advocated placing a ureteral catheter in the remnant pole and injecting indigo carmine dye at the conclusion to confirm closure. This is useful in partial nephrectomy in the adult without duplication, but probably is not necessary with duplication anomalies because the separation is usually clear.

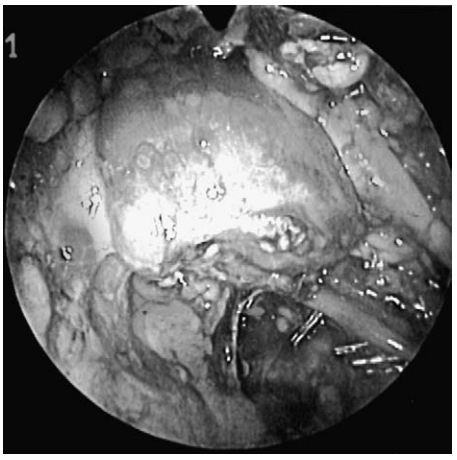

Fig. 4. The upper pole of a duplex kidney after lower-pole nephrectomy.

No attempt is made to suture the edge of the remnant pole, but with robotic assistance the author now does this to ensure hemostasis and limit the risk for leakage (Fig. 4). The author typically has not drained the bed in small children, but recommends drainage in older children or in complex cases. A bladder catheter is left in place overnight, although some children have been discharged on the same day.

Urachal cysts

Several reports of urachal cyst resections have been published, although it is unclear if this technique is useful [22,23]. It transforms a preperitoneal procedure into an intraperitoneal one. The usual open access through the umbilicus is a minimal incision with no visible scar, whereas laparoscopically, two extra small incisions would be needed. The author has not recommended using this procedure, although he has performed a few. This technique may be appropriate in a child with umbilical drainage and an uncertain diagnosis. If the drainage is a result of an omphalomesenteric duct or omental hernia, then laparoscopic diagnosis and subsequent therapy is efficient, including if the diagnosis is a urachal anomaly.

Gondectomy and Müllerian remnants

Following diagnostic assessment of abnormal or inappropriate gonadal or Müllerian structures, it is possible to collect a biopsy of the indeterminate gonad or remove the inappropriate gonad without much further invasiveness [24]. Resection of Müllerian structures also is accomplished readily laparoscopically [25], and is particularly efficient in the deep pelvis behind the bladder, a difficult area to access with open surgery. Although not strictly intersex conditions, cases with abnormal Müllerian structures, such as seminal vesicle cysts, are well managed with laparoscopic excision (Fig. 5) [26].

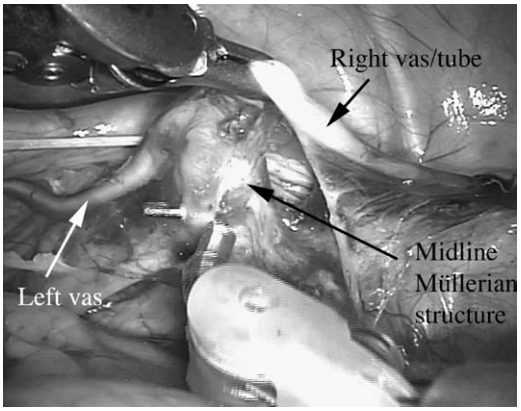

Fig. 5. Laparoscopic excision of a Müllerian remnant in child with ring-Y chromosomal abnormality, dysgenetic gonad, and urinary infections. This structure included histologic patterns consistent with vagina and uterus.

Reconstructive surgery

Orchiopexy

Laparoscopic orchiopexy is one of the best-described and useful applications of laparoscopic techniques in children. Solid data support its efficacy and it may be better than open orchiopexy [27]. This conclusion will be limited because the true outcome of any orchiopexy, fertility in adulthood, has never been assessed well [28]. Recognizing that limitation, however, the data are strongly positive. Laparoscopic orchiopexy also is integrated well with the diagnostic procedure and allows progressive learning by the surgeon with developing laparoscopic skills and experience.

Indications

Laparoscopic orchiopexy is used for the intra-abdominal testis. This procedure almost always is performed at the same time as the diagnostic laparoscopy that identifies the testis and determines its location. The transinguinal testis has been treated with laparoscopic orchiopexy [29], but it is unclear if this represents an advantage, and the author has not used laparoscopy in those cases. It could be argued that intra-abdominal dissection and mobilization may facilitate subsequent open orchiopexy, which may be a useful adjunctive role for surgical laparoscopy.

Laparoscopic orchiopexy can be either a single-stage or primary orchiopexy leaving the spermatic vessels intact, or a staged Fowler-Stephens orchiopexy. The latter is reserved for testes that appear unable to be brought into the scrotum with the spermatic vessels intact. In these patients, initially the spermatic vessels are occluded, usually with a clip or suture, or by fulguration. The testis is left in place and at least 4 months later, the testis is mobilized to the scrotum on a pedicle of the vas deferens and peritoneum with the spermatic vessels having been transected. Some have advocated a single-stage Fowler-Stephens procedure, but the outcomes seem unacceptable and it cannot be recommended [30,31].

Technique

Position. The patient is supine with legs slightly parted and a bladder catheter in position from the sterile field. It is best to drape the catheter off the contralateral side to prevent its being in the way when working at the scrotal level. The patient is placed in moderate Trendelenberg position with the ipsilateral side rotated upward approximately 30° to 45°.

Ports. The initial diagnostic port is in the umbilicus, and once the testis is identified and a decision made to proceed with surgical orchiopexy, it can be changed to a different size. The author routinely performs the initial diagnosis with a 2-mm single-pass Veress introducer and the 2-mm endoscope, which can be up-sized to 3.5 mm for operative manipulation. Working ports (usually 3.5 mm) are placed in the ipsilateral upper quadrant and the contralateral lower quadrant (Fig. 6) under direct vision. All ports will be closed and the fascial closure stitch usually is placed with the cannula to facilitate the end of the procedure.

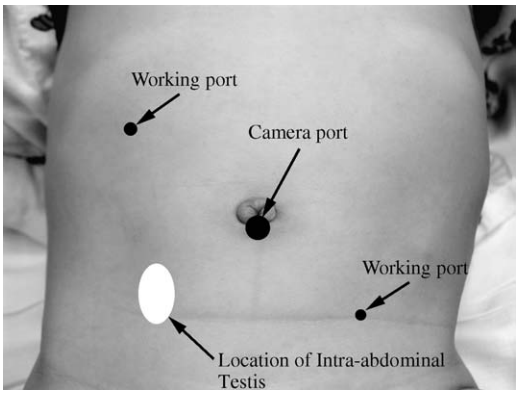

Fig. 6. Port placement for unilateral, right-sided laparoscopic orchiopexy. The ipsilateral port needs to be in the upper quadrant to prevent limited mobility during proximal dissection of the spermatic vessels.

If a two-stage orchiopexy is indicated, the vessels are clipped after creating a window in the peritoneum 1 to 2 cm above the testis, and the clips are placed around the vessel through this window. This requires only one working port in the contralateral lower quadrant.

Instruments. There is little need for complex instruments for laparoscopic orchiopexy. The author uses 3.5-mm tools and finds that a cauterizing scissor and a curved dissector are adequate. The testis is brought into the scrotum from the abdomen using a long, gently curved vascular clamp. If clips are placed, the author uses a 5-mm clip applier. The curved dissecting instrument is used to create the passage from the pelvis into the scrotum and a long, curved vascular clamp is passed retrograde by grasping the tip of the dissecting instrument.

Procedure. Following placement of the working ports and instruments, dissection begins by incising the peritoneum lateral to the spermatic vessels and mobilizing down to the inguinal ring. The gubernacular attachments are taken down to the ring with care to avoid injuring a possible long-looping vas deferens. Once the distal gubernaculums has been transected, it is used as a handle to move the testis, and the lateral dissection continues cephalad over the iliac vessels and under the intestines. The testis and the pedicle are swept off the pelvic sidewall and the peritoneum lateral to the vas is incised down into the deep pelvis.

This leaves a triangular web of peritoneum between the vas and the vessels with the testis at the apex. Some authors suggest leaving this web intact to preserve the blood supply of the vas, but it distinctly hinders mobilization of the testis. The author therefore incises it, mobilizes the spermatic vessels cephalad, and then transects the bridge of peritoneum between the medial and lateral lines of dissection parallel to the spermatic vessels. This releases the vessels well.

Once the testis has been mobilized enough to be moved to the opposite inguinal ring, the author develops the pathway over the pubic tubercle into the scrotum. A dartos pouch is developed first and then the curved dissecting instrument is passed using direct vision and finger palpation, medial to the obliterated umbilical artery and lateral to the bladder. The tip of the dissector is guided into the scrotal sac and pushed through. The curved dissecting instrument is used to create the passage from the pelvis into the scrotum and the long, curved vascular clamp is passed retrograde by grasping the tip of the dissecting instrument. The clamp can be spread to open the passage for the testis to move through.

The testis is grasped and brought into the scrotum where it is fixed in place in whichever manner is preferred. If there is tension on the vessels, further mobilization may be performed with the testis being retracted from the scrotum.

Results. There are several reports of the outcomes of laparoscopic orchiopexy [27,31,32]. The outcomes parameters are somewhat subjective, although not different than those used for assessing open orchiopexy. Because there has been no long-term assessment of any orchiopexy techniques, the short-term assessment by the operating surgeon will have to suffice. It is important to have at least 6 to 12 months of follow-up with an examination because some testes in the author's series had no apparent atrophy at 6 months, but appreciably reduced in size by 12 months. The author has used Doppler ultrasound to assess testicular size and blood flow, which seems to correlate with examination.

In general, results have been good in most series. A multi-institutional report has been published [27]. There are no real standards of assessment of initial location or of postoperative outcome. It likely is safe to consider success rates of approximately 95% for patients with intra-abdominal testes undergoing single-stage orchiopexy with the vessels intact and approximately 90% for patients undergoing Fowler-Stephens orchiopexy. These rates are better than that for open orchiopexy, but the correlation with initial position is unclear.

Age of the patient is likely to impact outcome. Any patient over 2 years of age with an intra-abdominal testis should have a two-stage orchiopexy because it is difficult to move those testes, regardless of initial position, into the scrotum.

Comment. Whether laparoscopic orchiopexy is better than open orchiopexy will be difficult to confirm with a prospective study because of the need for long-term outcomes and because it would be difficult to convince patients' families to choose an open procedure.

Hernia

Few surgeons have performed laparoscopic hernia repair, although there are several large series using this technique [33–35]. It may seem an

overly aggressive use of laparoscopy, but the methods used are efficient. If one is facile with suturing, the excellent exposure provided by laparoscopy permits precise suture placement, avoiding the vas and spermatic vessels and performing a purse-string closure of the hernia sac from within. The procedure can be performed using three punctures (ports are not needed in the small child) and the repair is completed in less than 15 minutes. Results are good, although there is a reported 3% recurrence rate. The author has had one recurrence, which suggests the technique may not be the optimal way to deal with hernias in children.

Pyeloplasty

The delicate suturing needed in pyeloplasty has been the major impediment to its widespread adoption. It has developed in pediatric practice slowly and few surgeons in North America have much experience [36]. The technique is practicable and the outcomes have been good in all but young patients [37,38]. Retroperitoneal access has developed and is technically efficient [39].

Port placement for transperitoneal pyeloplasty is similar to that for nephrectomy with an umbilical port: an upper quadrant port just lateral to the midline on the side of the affected kidney and an ipsilateral lower quadrant port (Fig. 7). A fourth holding port can be placed laterally. Retroperitoneal access is with three ports in line along the lower edge of the twelfth rib. Prone access is possible with a similar in-line port layout.

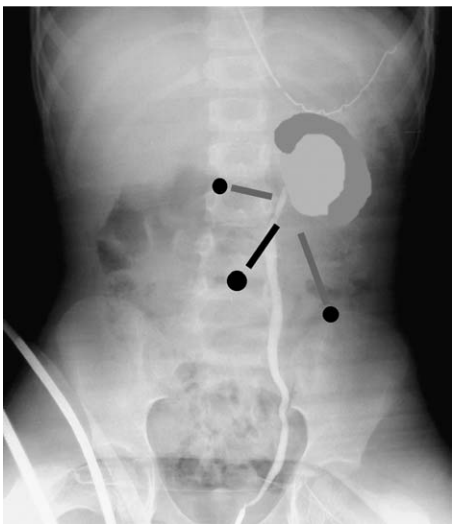

Fig. 7. Port placement for transperitoneal pyeloplasty on the left. The upper port should be near the midline. The isosceles triangle formed by the ports is directed toward the renal pelvis.

The method is essentially identical to the open procedure with exposure of the renal pelvis, but diverges in the placement of a hitch stitch to stabilize the pelvis. The author transects the pelvis first and uses it as a handle for the ureter to permit spatulation. Alternatives include placing a small traction stitch on the ureter after transecting distal to the uteropelvic junction or leaving a bridge of pelvic tissue on the medial aspect to stabilize the tissues. Accurate suturing is challenging, but with the enhanced visualization of the laparoscope, it is possible with practice. A stent can be left in place, as was the author's preference initially because it seemed that the sutures were never placed as accurately as with open surgery and a double-J stent eliminated the need for a drain.

Reported outcomes are good, but no better than open procedures. The morbidity seems less, however, particularly for older patients. Failures have been limited to small children (less than 6 months of age) or those with massive hydronephrosis.

Antireflux surgery

Initial attempts at antireflux surgery were clumsy and slow. The principle was based on the extravesical Lich-Gregoir operation [40] and was successful, but was too time-consuming to be advantageous; after an initial interest, few further attempts were made [41,42]. Interest renewed and a series of successful procedures was reported [43]. There were several significant early complications and hospital stays were long, but this has improved with experience. The procedure is performed transperitoneally with exposure of the distal ureter, incision of the detrusor muscle along the line of the ureter, and subsequent closure of the muscle over the ureter to create the antireflux tunnel. No attempt at ureteral advancement was made. The suturing was the most challenging aspect, in part because of the angle of approach. Bilateral procedures have been performed and the reported outcomes show none of the anticipated urinary retention, but the numbers are limited and the concern remains. Success seems to be equal to open surgery, although objectively demonstrating a clinical advantage will be difficult.

Intravesical antireflux surgery recently has emerged as an alternative with few practitioners

[44,45]. Several earlier attempts did not develop [46]. The advantage of intravesical antireflux surgery is that there is no peritoneal violation and there should be essentially no risk for urinary retention, as with open transvesical ureteral reimplantation. The technical challenges are mobilizing the ureter, creating the submucosal tunnel, and the suturing to implant the ureter. These are feasible in a few highly skilled hands, but it is questionable if most laparoscopists would undertake this operation. Again, demonstrating a clinical advantage will be difficult.

Robotically assisted laparoscopic antireflux surgery is a promising option for most practitioners. This is essentially the same operation using the extravesical approach, although the intravesical technique also has been used successfully. The laparoscopic approach seems most appropriate in the older child with reflux, in whom even the lower abdominal incision is uncomfortable. Operative times are reasonable, about 2.5 hours, and most patients have been discharged in 24 hours.

Continent diversion and augmentation

The major challenges of laparoscopy will lie in the major reconstructive operations of pediatric urology. Laparoscopic procedures may show their major benefit in all age groups in these procedures with substantial morbidity of access. A reasonable first attempt is creation of an appendiceal continent catheterizable stoma (Mitrofanoff) because the limited suturing is efficient (Fig. 8). Jordan [47] reported an unusual case of this in 1993; there have been few subsequent reports. Robotic assistance can provide a major advantage by making the delicate suturing efficient. Docimo and colleagues [48,49] have advocated in several reports integrating laparoscopic mobilization with a more limited open incision to complete the procedure, with excellent results for an important concept. This approach may serve as a bridge for developing skills and providing adequate care of patients.

The ability to perform an entire reconstruction with augmentation and continent stoma formation exists technically [50], but is not practical until efficient means of suturing and reconstruction are developed. Such means may include alternatives to suturing, such as tissue glues or welding, or the use of robotic assistance to suture. New algorithms of harvesting bowel segments to use in the reconstruction also will be required.

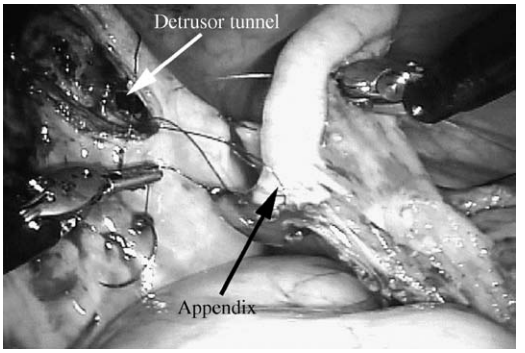

Fig. 8. Creation of appendiceal continent catheterizable stoma (Mitrofanoff) with robotic assistance in a boy with bladder dysfunction caused by posterior urethral valves. The appendix is being mobilized to the bladder; the trough in the detrusor will become the continence mechanism.

Horizons

Emerging role of robotic surgery in laparoscopy

The most exciting prospect on the laparoscopic horizon is surgical robotic technology. There is substantial experience in gastrointestinal, thoracic, cardiac, and adult urologic endoscopic surgery using the robotic devices [51–53]. The principal advantage is the markedly enhanced ability to perform precise suturing for reconstruction, supported by enhanced visualization with three-dimensionality and the remarkable dexterity of wrist technology that is integral to the suturing capability.

The most widely used system is the DaVinci (Intuitive Surgical, Sunnyvale, California), which has three parts: (1) the endoscope and manipulative arms mounted on a large pedestal at the bedside, (2) a surgeon's console with the image monitor and manipulator controls, and (3) an instrument tower holding controls and a monitor for the patient-side staff to follow the procedure. Instruments, including scissors, dissecting and grasping tools, and needle holders, as well as a harmonic scalpel, are mounted on the manipulating arms and passed through laparoscopic cannulae. The patient-side staff exchanges instruments for differing tasks or passing sutures into the field.

The limited experience in children has been developing, and the first cases seem promising. The author has used the instrument to perform extra- and intravesical ureteral reimplants for reflux (Fig. 9), pyeloplasty (Fig. 10), nephrectomy, continent diversion with appendix, and

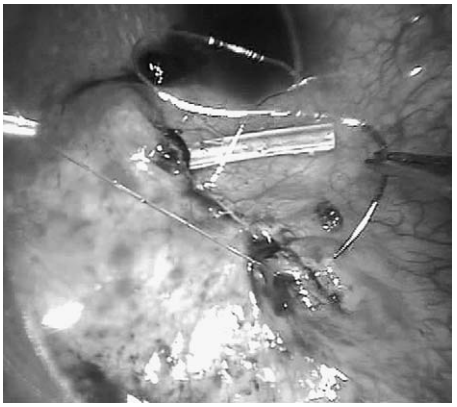

Fig. 9. Completion of intravesical, robotically assisted, laparoscopic, transtrigonal ureteral reimplantation in a child. Cannulae are placed directly into the bladder, which is insufflated with CO_2.

pyelolithotomy. The manipulative ability is good, and far better than that of conventional laparoscopy. Similarly, visualization is much enhanced. The instrument is large and the port sizes are 12 mm and 8 mm. Five-millimeter working ports will be in use shortly. The 12-mm port is hidden easily in the umbilicus and the scars from the other ports seem to be limited. The author has used the instrument in children as young as 5 months of age, but the working space is limited. Cost is a major impediment, but this will improve, much as computers with improved capabilities have become available readily. It will be critical, however, for practitioners to guide that development and not wait until it has occurred, which would necessitate accommodating rather than defining the technology.

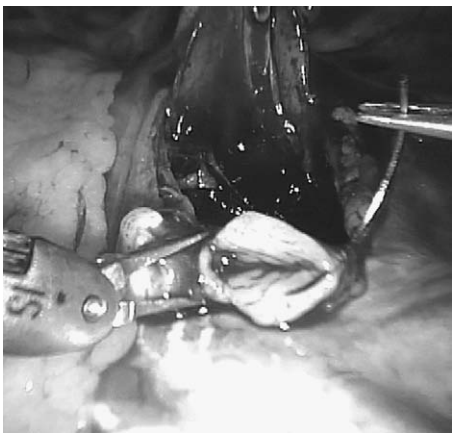

Fig. 10. Laparoscopic pyeloplasty with robotic assistance. The anastomosis is begun with placement of a 5-0 monocryl suture at the vertex of the ureteral spatulation.

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Renal and adrenal tumors in children

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Although tumors of the kidney in children had been described sporadically in the medical literature, Max Wilms, a German surgeon, described their common histologic features. Before 1930, the outlook for these patients was poor, and most died of their disease or attempted surgical intervention. Ramon Guiteras [1] noted in his textbook of urology in 1913 that tumors of the kidney in a child were virtually always fatal. At the start of the new millennium, survival rates for these patients approach 90%, even for the most advanced stages of disease. The path of the past 50 years that improved survival dramatically is worth retracing [2].

Advances in anesthetic and surgical technology and techniques made an incredible difference in the ability of children to survive the surgical procedure. Even today, under more optimal conditions, the surgical management of large lesions remains challenging [3]. Sidney Farber's [4] observation that chemotherapy could eradicate tumor was a quantum leap forward. Some patients with pulmonary metastases were administered actinomycin D, but died of their advanced disease. At autopsy, however, the pulmonary lesions contained fibrosis and no evidence of tumor, giving medical oncologists hope that such treatment would benefit future patients. With the development of additional chemotherapeutic regimens and the use of radiation therapy, survival rates began to improve dramatically for these children [2], and it became evident that not all patients would require intensive therapy. Hence, the need for carefully designed trials. With only 400 cases of Wilms' tumor presenting each year in the United States, it was apparent that only a national, cooperative study could provide answers in a timely fashion. The National Wilms' Tumor Study (NWTS) was organized in response, and has conducted four long-term studies [5–8] addressing how adjunctive therapy may be tailored optimally to maximize survival and minimize the exposure to chemotherapy and radiation therapy.

Diagnostic imaging

Radiographic studies are essential to identify in advance special circumstances in which the surgical approach will differ from the traditional simple nephrectomy. Such conditions would include the presence of tumor extension into the vena cava, bilateral disease, or a malignancy in a solitary kidney. The evaluation of these patients usually begins with an abdominal pelvic ultrasound ordered by a referring physician. Whenever possible, the radiologist should be consulted in advance as to the suspected diagnosis, so that additional views may be taken of the inferior vena cava to establish the presence or absence of tumor thrombus. A CT scan with contrast establishes the presence of function in the contralateral kidney and rules in any evidence of bilateral disease. Chest films with oblique views or a CT scan of the chest are indicated to rule out pulmonary metastases.

Staging

Despite the impressive advances in diagnostic imaging, the staging of Wilms' tumor is based on clinical observations made in the operating room and ultimately in the pathology suite. It was crucial to the success of the NWTS that a common terminology existed for patient stratification (Table 1). Despite the size of the tumors and

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Table 1
Staging classification adopted by the National Wilms Tumor Study group and current adjuvant therapy recommendations

NWTS stage	Description	Chemotherapy	Radiation	Survival RFS (overall)
I	Completely contained within renal parenchyma	AMD + VCR 18 weeks	No	90% (97%)
II	Capsular margin (+)	AMD + VCR 18 weeks if favorable histology Add DOX + CPM and etoposide if histology shows anaplasia	No Except if unfavorable histology	89% (93%)
III	Nodes (+)	AMD + VCR + DOX 24 weeks if favorable histology Add CPM and etoposide if histology shows anaplasia	Yes	74% (85%)
IV	Visceral/pulmonary metastases	AMD + VCR + DOX 24 weeks if favorable histology Add CPM and etoposide if histology shows anaplasia	Yes	69% (81%)
V	Bilateral renal involvement	Biopsy to confirm, then AMD + VCR 8–12 weeks Repeat CT scan Add third agent if no response	Yes	75% (73%)

Abbreviations: AMD, actinomycin D; DOX, doxorubicin; CPM, cyclophosphamide; RFS, recurrence-free survival (tumor-free survival) VCR, vincristine.

Data from: Refs. [12,13,20,21].

changes in lymph nodes, final staging is determined by histologic analysis of the renal margins and nodal status. These two parameters greatly affect subsequent adjuvant therapy. It is important that the contralateral kidney is examined with direct visual inspection of the anterior and posterior surface to search for evidence of nephrogenic rests and small tumors that may evade detection by CT or MRI in up to 7% of cases (although with current imaging, this point is debated) [9].

Surgical considerations

Additional preoperative testing should include a complete blood cell count, electrolytes with blood urea nitrogen and creatinine, liver function tests, and type and crossmatch. No matter how routine the nephrectomy may appear on a CT scan, acute hemorrhage can be rapid, and blood always must be available. These tumors typically present as large abdominal masses, and the surgical approach to the renal artery often is complicated by numerous dilated veinous collaterals. The traditional surgical approach to these patients is transperitoneal with an incision large enough to allow for exploration of the contralateral kidney. Upon entering the peritoneum, the opposite kidney is exposed and inspected for small capsular lesions that may have evaded detection by preoperative imaging. Although CT and MRI have made it possible to detect more than 95% of contralateral lesions, the NWTS continues to advocate contralateral exploration given the difference in management for patients with bilateral disease. Therefore, any suspicious lesions in the contralateral kidney should be biopsied before proceeding with nephrectomy.

Once the contralateral kidney is cleared as normal, attention is directed to identifying the major vessels leading to the ipsilateral affected kidney. The vein should be inspected carefully to ensure that no tumor thrombus is present. After ligation of the artery followed by the vein, a nephrectomy is performed, with the surgical team noting the extent of the tumor margins. Upon removal of the specimen, a sampling of the lymph

nodes should be taken, with a special emphasis on any enlarged nodes, 50% of which will contain tumor on histologic examination. All specimens should be delivered to the pathology suite with a detailed map showing the locations of the primary tumor, a description of the margins, and from where the lymph nodes were sampled.

Surgical management of Wilms' tumor is challenging because of the large size of the primary lesions. Because pretreatment with chemotherapy may lead to understaging of patients, management in the United States has called for exploration, nephrectomy, and lymph-node sampling as the initial management. Even in the fourth NWTS, 11% of patients experienced surgical complications, most commonly hemorrhage and bowel obstruction postoperatively [10]. Another important surgical goal is to avoid tumor rupture and spillage because it increases local recurrence rates up to sixfold [11]. In summary, the surgeon's goals are to (1) eliminate or diminish tumor burden, (2) accurately stage the extent of disease, and (3) minimize the need for additional chemotherapy or radiation therapy by avoiding tumor spillage.

Adjunct therapy stage by stage

A major achievement of the NWTS has been survival rates of over 80% for all stages, and continuing to minimize the toxicity of chemotherapy and radiation therapy. The decisions about adjunctive therapy are made by considering the stage and histologic grade, and Table 1 summarizes the current NWTS 5 recommendations. For patients with stage I or II favorable histology, an 18-week course of actinomycin D and vincristine has produced survival rates of 100%. If the pathologist reports the presence of anaplasia, the complexity of the regimen increases, and radiation therapy is added irrespective of stage. The use of doxorubicin is restricted to patients with stage-III disease or higher, or those with anaplasia. Another goal of the current NWTS is to validate molecular markers, such as the loss of heterozygosity for chromosomes 16q and 1p, that can better predict which patients are at greater risk for relapse and identify new potential markers [12].

National Wilms' Tumor Study versus International Society for Pediatric Oncology trials

The approach to a patient with Wilms' tumor varies among institutions; most European centers have adopted a trial of biopsy followed by chemotherapy upfront (International Society for Pediatric Oncology—SIOP trial). Following medical reduction of the tumor burden, a nephrectomy and lymph-node sampling is performed. This is in contrast to most American institutions, in which the approach advocated by the NWTS is standard. How do outcomes compare between these two approaches?

D'Angio [13] has outlined the major advantages and disadvantages of both approaches succinctly. The two trials cannot be compared directly because the patients in the NWTS are staged surgically. This is a crucial point. It does not matter which approach is taken for patients who have true stage-I disease because for these two trials, the therapy is the same. For patients who have stage-III disease, however (ie, those with positive lymph nodes), failure to treat patients with positive nodes has resulted in a higher rate of local recurrence. A major concern with up-front chemotherapy is that positive lymph nodes will be rendered tumor-free, thus preventing accurate staging. The SIOP trial addresses this concern by treating all patients with capsular extension (stage II) with a course of anthracyclines, even if their lymph nodes are negative. Thus, critics of the SIOP approach argue that many patients with true stage-II disease are subjected to the potential toxicity of anthracylines without a benefit. This argument is countered by proponents of preoperative chemotherapy, who point out that there is a higher risk for tumor spillage during a nephrectomy performed as first-line therapy, which in turn increases the risk for local recurrence by 10% [11]. This increase, however, did not translate into a significant increase in mortality.

Both of these trials have produced remarkable occurrence-free and total survival. The NWTS approach is favored in the United States because it can obtain a more exact surgical staging that allows therapy to be tailored to minimize long-term side effects. This is crucial because long-term follow-up in this patient population is 60 to 80 years. In one study of long-term outcomes following doxorubicin administration, the incidence of congestive heart failure (CHF) was 20% approximately 20 years after therapy [14]. Will this percentage increase as this cohort of patients ages? Will these rates of CHF decline as the doses of doxorubicin are dropped to the lowest levels possible?

Another study has shown that adult survivors of Wilms' tumor are more likely to develop a second malignancy [15]. Another recent report

described four adult patients who developed a tumor in their remaining kidney years after their initial therapy for Wilms' tumor [16]. These authors questioned if the incidence of such findings will increase as more long-term survivors reach adulthood, and speculated that if there is a rise in such findings, an argument could be made for partial nephrectomy as the initial management for these children. This report describes a highly selected patient population because it comes from a center known for its expertise in nephron-sparing surgery. Further long-term outcomes studies must examine the frequency with which such tumors develop in the contralateral kidney in a complete cohort of NWTS patients. Currently, with an experienced surgical, anesthesia, and medical oncology team in place, an argument can be made for an up-front nephrectomy and lymph-node sampling [13]. It is equally important to remember when exceptions to this approach should be taken, and a SIOP-type protocol adopted, as in the following examples.

Special surgical considerations

Rarely, special circumstances such as caval extension, bilateral disease, or a tumor in a solitary kidney arise in which the patient should be pretreated with chemotherapy before definitive surgical resection. Pretreatment dramatically reduces tumor thrombus for patients with caval extension, which will reduce substantially the surgical morbidity [17]. Patients with bilateral disease or tumor in a solitary kidney should be managed with a biopsy, and under certain circumstances, a lymph-node sampling followed by chemotherapy. Chemotherapy administered up-front usually reduces tumor burden substantially, making the partial nephrectomies simpler to perform. Several cases illustrate the application of these general principles.

A 5-year-old boy presented with a solid mass in his right lower quadrant. A CT scan revealed an 8-cm solid mass in the kidney that was a crossed fused ectopia (Fig. 1). An open biopsy and lymph-node sampling confirmed Wilms' tumor and that the nodes were tumor-free. The patient was treated up-front with actinomycin D and vincristine, and there was a substantial reduction in tumor burden at 10 weeks. A partial nephrectomy was performed and the specimen's margins were tumor-free.

A 6-year-old boy presented with a slowly expanding mass in his right kidney; 1 year earlier, he had undergone a left nephrectomy for Wilms' tumor (Fig. 2). The presumptive diagnosis was that this also represented Wilm's tumor, and the decision was made to proceed with a partial nephrectomy. Following mobilization of the kidney, the vessels were isolated, mannitol was administered, and regional hypothermia was applied with an ice slush contained within a rubber dam [18]. Once the parenchyma was cooled, the vessels were clamped, the tumor was excised, and the size of the cavity was measured. A Foley catheter balloon was inflated to these dimensions, and placed within the cavity, which was then closed over the balloon. Three days later, the tumor bed was treated with brachtherapy administered through the catheter in the form of iridium seeds. The dosimetry calculation was based on of the dimensions of the cavity and Foley balloon, which had been determined intraoperatively [19]. Despite negative tumor margins on the specimen, the decision was to proceed with the brachytherapy because of the possibility of sampling error, and concerns for local recurrence. Eight years later, this patient remains tumor-free with a normal serum creatinine.

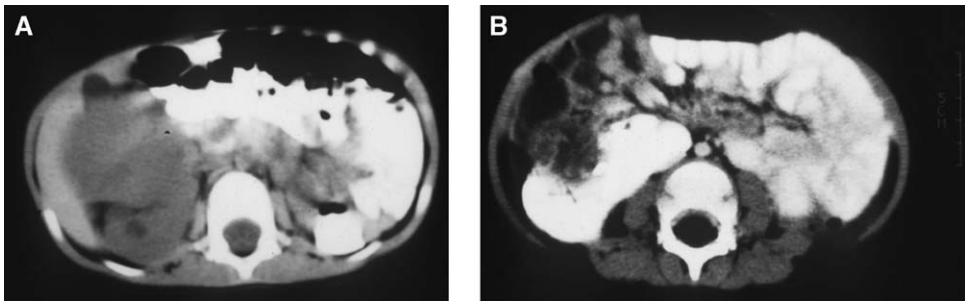

Fig. 1. (*A*) Patient presented with a right-sided abdominal mass that biopsy showed to be a Wilms' tumor in a cross-fused ectopia. The tumor responded well to chemotherapy with actinomycin D and vincristine (*B*), and the patient underwent a successful partial nephrectomy.

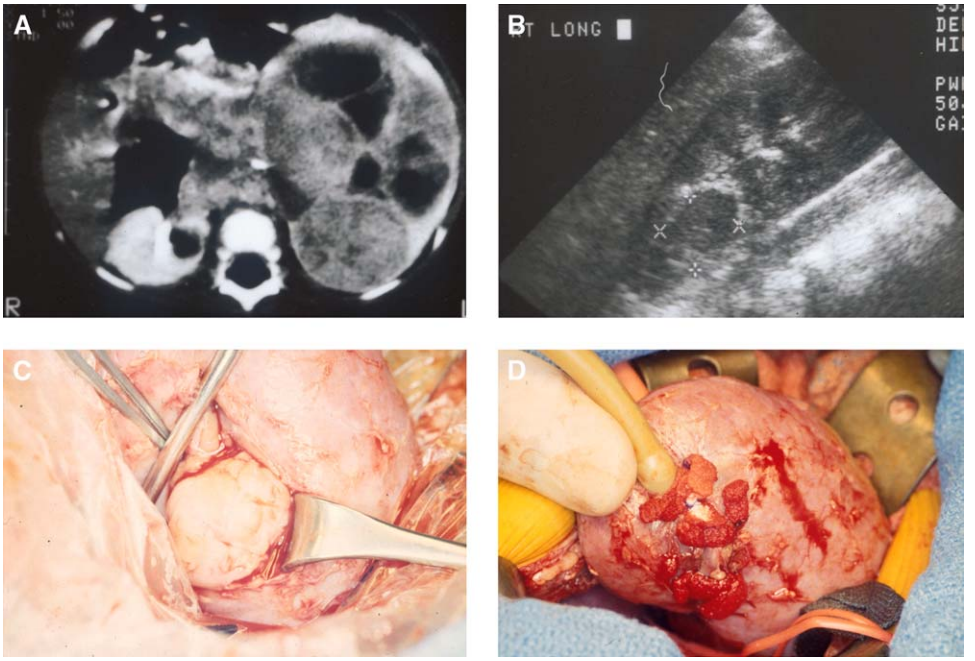

Fig. 2. Patient presented with a left-sided abdominal mass (*A*), and underwent a left nephrectomy for a Wilms' tumor with favorable histology. The right-sided mass was observed, but grew, and the patient was referred for treatment of an expanding solid mass in a solitary right kidney (*B*). This lesion was enucleated (*C*), and a Foley catheter was left in the cavity with known dimensions through which brachytherapy was administered (*D*) [19,21].

A 3-year-old girl presented with a huge abdominal mass that on CT scan was shown to represent bilateral renal tumors (Fig. 3). The presumptive diagnosis of Wilms' tumor was made, and the decision was made to proceed with chemotherapy without a biopsy. Despite an aggressive regimen of chemotherapy, there was no change in the size of these masses 8 weeks later, and the decision was made to proceed with bilateral partial nephrectomies. Bilateral indwelling catheters were left to administer brachytherapy postoperatively, and the patient remained free of residual tumor for 2 years. She presented to the emergency department 2 years later, however, with facial edema and was hypertensive with a serum creatinine of 7.0. No element of obstructive uropathy could be detected, and microscopic hematuria and massive proteinuria were noted on urinalysis.

Fig. 3. Bilateral Wilms' tumors in an 18-month-old girl who was treated with chemotherapy to shrink the rumor burden. Although the tumors did not respond to chemotherapy, she underwent successful partial nephrectomies. This patient ultimately was shown to have Denys Drasch syndrome.

A clinical diagnosis of end stage renal disease secondary to Deny's Drasch syndrome was made, which was confirmed on pathologic examination of the kidneys that were removed when her peritoneal dialysis catheter was placed. Histopathologic evaluation of the kidneys showed signs of diffuse mesangial sclerosis. The classic triad of the Deny's Drasch syndrome includes genital ambiguity, a progressive glomerulopathy, and the development of Wilm's tumor. This syndrome is diagnosed more readily in males as a result of the evaluation of ambiguous genitalia. As this case illustrates, it

can present in females, most often as bilateral Wilms' tumors. Given the known mutation in the *WT-1* gene that has been mapped to chromosome 11p13, a molecular diagnosis should allow more effective management of these patients, including the use of up-front nephrectomies before the onset of malignancy. The challenge of identifying this syndrome in the rare genotypic and phenotypic female will remain.

In summary, children with solitary kidneys or bilateral disease may be managed with nephron-sparing techniques and achieve equivalent survival to other patients in the NWTS [20]. In a review of the Children's Hospital of Philadelphia's experience with nephron-sparing surgery, the key determinant of patient survival was the histologic classification of the tumors [21]. Patients whose tumors were characterized as having unfavorable histologic elements fared more poorly than their counterparts with favorable histology, irrespective of stage. Another factor to be considered is the frequency of recurrences. Several rare instances have been noted of patients who, despite initial favorable histology, had several recurrences until the histology changed to unfavorable elements. It is hoped that with a better understanding of the molecular biology of these tumors, this subset of patients can be identified reliably and undergo up-front nephrectomies and transplantation in the future.

Sarcoma and rhabdoid variants

In years past, sarcoma and rhabdoid variants were included in the category of Wilms' tumors, but it is now clear that they have differing cellular origins. These tumors have differing metastatic potential, and a far more ominous prognosis [22]. The classic location for clear cell metastases is bone; in contrast, rhabdoid tumors may metastasize to brain. The rhabdoid renal tumor accounts for 2% of pediatric renal tumors. This highly malignant tumor presents in young patients with a mean age of 13 months, and is cured reliably only in the early stages. For patients with a rhabdoid tumor and positive lymph nodes, the 2-year survival rate is reported to be as low as 10% [23], although recently several long-term survivors have been reported [24]. Patients with a rhabdoid tumor often present with gross hematuria and may exhibit hypercalcemia and calcifications within the kidney that are often prominent (Fig. 4) [25].

Renal-cell carcinoma

Renal-cell carcinoma is observed in childhood, and is the more likely diagnosis when a patient presents with a renal mass after 8 years of age. Gross hematuria is more common with this tumor than with Wilms' tumor. As in adults, radical nephrectomy offers the only effective means of management. There is no effective medical adjuvant therapy for patients with renal-cell carcinoma, irrespective of age.

Angiomyolipoma

Angiomyolipoma is a rare renal tumor most likely to present in children who carry a known diagnosis of the tuberous sclerosis complex (TSC) [26]. Although these tumors are benign, they may cause substantial morbidity if their size may cause hemorrhage. For this reason, annual ultrasound examinations are recommended. In older patients, obesity may prevent the use of ultrasound, and serial MRIs may become needed for follow-up

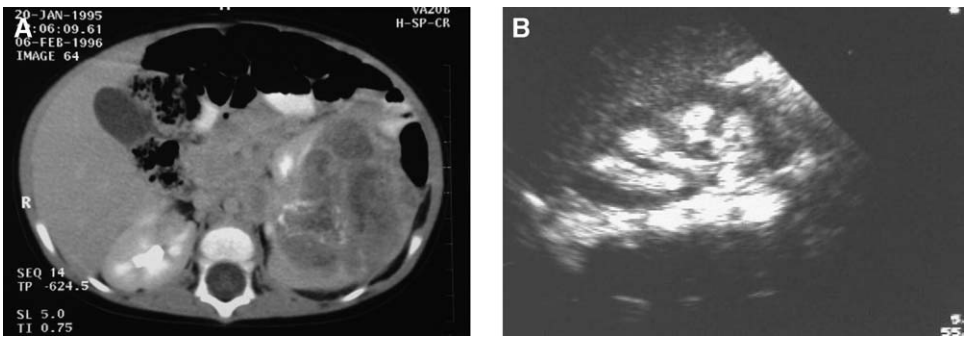

Fig. 4. Rhabdoid tumor in an 8-month-old girl who developed gross hematuria. The large left renal tumor was calcified (*A*), as were the medullary regions of her right kidney (*B*). Hypercalcemia was present, and is noted in 25% of these tumors. Despite positive lymph nodes, she is alive 8 years later following aggressive chemotherapy and radiation therapy.

studies (Fig. 5). Studies have shown that over 50% of patients with TSC develop angiomyolipomas by an average of 7 years of age [27]. For lesions greater than 4 cm in diameter, the risk for hemorrhage increases [28], and the use of selective embolization has been effective. On occasion, open exploration with partial nephrectomy will be required for a lesion whose growth persists despite embolization. Careful follow-up is important because rare cases of renal-cell carcinoma (see Fig. 5) will appear in this population [29].

Adrenal tumors

Neuroblastoma

Neuroblastoma is the most common extracranial solid neoplasm found in children. One of the more intriguing features of this tumor is the frequency with which it is identified in fetal adrenal specimens. Studies suggest that in early fetal development, all adrenals contain focal areas with histology consistent with neuroblastoma [30]. The much lower incidence of clinical neuroblastoma suggests that most of these lesions will involute. Clinical presentations may include the finding of an abdominal mass, bone pain secondary to a metastasis, or anemia caused by bone-marrow tumor infiltration. Although most neuroblastomas arise from the adrenal glands, these tumors may develop anywhere along the sympathetic chain, which accounts for the occasional symptoms that are secondary to catecholamine release. Thoracic lesions, pelvic masses arising from the organ of Zuckerkandl, and direct compression of the spinal cord are also possible presenting sites.

Most patients will have an initial ultrasound evaluation that documents the presence of an adrenal mass. CT scans of the abdomen, pelvis, and chest document the degree of spread and lymphatic involvement. The use of I-131 metaiodobenzylguanadine has been described as a functional imaging approach to detect lymphatic spread. Urinary levels of vanillylmandelic acid and homovanyllic acid are elevated in 90% or more of these patients at the time of presentation, and these levels drop with therapy, which offers oncologists a noninvasive means of searching for recurrences.

The traditional means of staging these patients was based on anatomic considerations, such as whether the tumor was localized or spread across the midline, lymph-node status broken down as local or distant, and whether the lesion was deemed unresectable. This traditional scheme worked well for patients with minimal or advanced stages of disease, but it failed to predict the outcome adequately for many patients. Shimada [31] developed a histologic classification system to further stratify these patients into those at higher risk for recurrence [32].

In the 1980s, neuroblastoma samples were analyzed for expression of the *N-myc* oncogene, which was increased in patients with advanced disease [33]. Despite this association, there are still

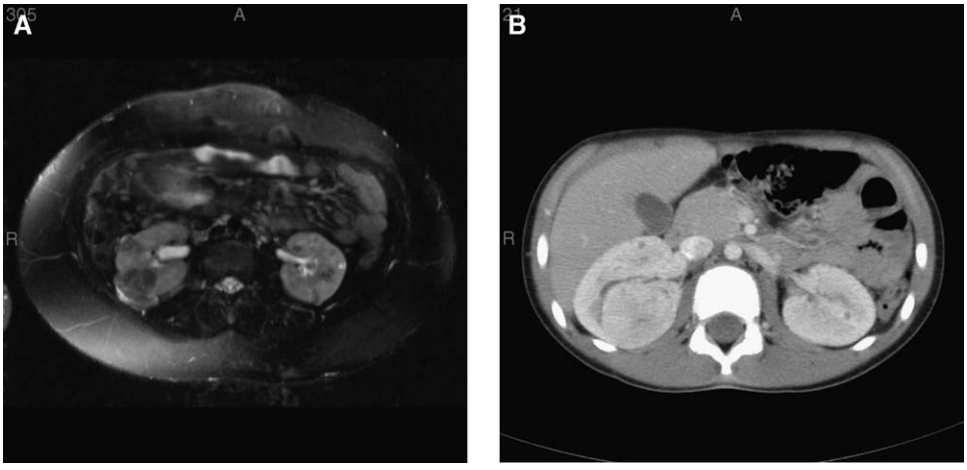

Fig. 5. Examples of two patients with tuberous sclerosis and bilateral angiomyolipmas that have grown with age. The large, right-sided angiomyolipoma is just under 4 cm in size, and if it expands further, angiographic embolization will be indicated (*A*). In a different patient, the lack of fat densities and rapid growth of the lesion raised concerns about renal-cell carcinoma, which was confirmed at surgical exploration (*B*).

many patients with advanced disease who present with no increase in *N-myc* expression, implying that there is a substantial degree of tumor heterogeneity. Clearly, however, *N-myc* amplification is associated with a poor prognosis independent of the patient's age or stage at presentation. In recent years, pediatric oncologists have relied on a strategy to categorize patients into low-, intermediate-, and high-risk groups by using traditional staging, patient age, *N-myc* amplification status, the DNA index (a measure of dipoloid versus the tetraploid states), and the Shimada histopathology grade. This risk scale better selects patients in need of maximal adjuvant therapy, and allows exclusion of patients in whom a surgical resection alone will prove curative.

The surgical excision of the tumor in a patient 1 year of age or younger with stage-1 disease and no *N-myc* amplification results in disease-free survival rates of 90% [34,35]. For these patients, chemotherapy and radiation therapy are indicated only for recurrences, which are rare. For patients with lymphatic involvement, or disease that has crossed the midline, an aggressive surgical resection will be followed by chemotherapy. This aggressive pursuit of tumor burden, however, should never come at the expense of normal adjacent structures. If surgical resection will compromise adjacent organs or large vessels, then the best debulking that can be attained or a biopsy should be followed by chemotherapy (Fig. 6). After repeat imaging to monitor the degree to which tumor burden has been diminished, a second laparotomy may be undertaken to provide the maximal degree of resection possible.

As the number of risk factors increases, the patient will be classified into the high risk of recurrence group, for whom the most aggressive chemotherapy is administered, as well as radiation therapy. In selected cases, intraoperative radiation therapy has been used. In some centers, autologous bone-marrow transplantation has been used as a last resort for patients in whom established chemotherapy regimens have failed [36]. For patients with stage-IV disease, an unfavorable Shimada classification, and an increase in *N-myc* copy numbers, the survival rate at 4 years is 20%, which underscores the need for such aggressive therapy.

An unusual manifestation of neuroblastoma is seen in the neonate who presents with stage-IV disease. Neonatal patients will have an abdominal mass, positive lymph nodes, subcutaneous tumor nodules, and evidence of hepatosplenomegally. Despite the findings of widespread disease, these patients often show spontaneous regression, even in the absence of any therapy [37]. With the application of modern molecular tools to these tumors, it seems that these patients have favorable prognostic factors. These patients with stage-IV disease must represent a different molecular etiology because their survival rate is 85% to 90% compared with the 20% rate seen in older patients with stage-IV disease.

Adrenocortical carcinoma

Adrenocortical carcinoma rarely presents in childhood, but its unique endocrine manifestations should be reviewed [38]. One third of patients with adrenocortical carcinoma will present with *Cushing's syndrome*, a manifestation of excess adrenal activity characterized by combinations of obesity, abdominal striae, moon facies, acne, fractures (secondary to osteoporosis), hypertension, and

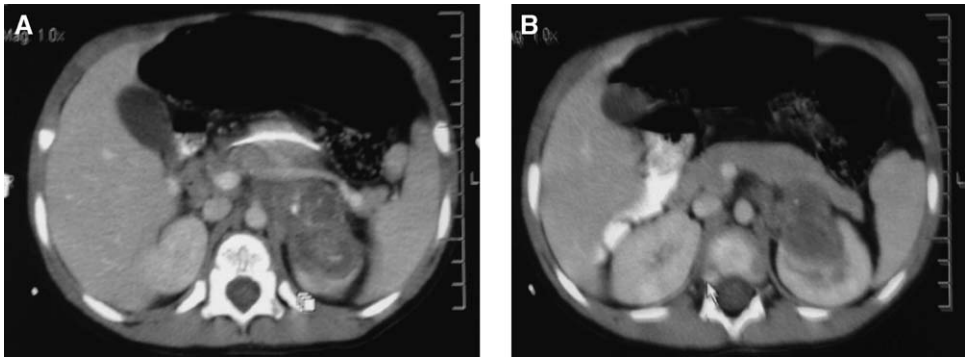

Fig. 6. These cross-sections demonstrate a large, left-sided neuroblastoma that has invaded the left renal parenchyma and persisted despite chemotherapy. This tumor was removed successfully, and the left kidney was preserved using an enucleation technique. (Courtesy of P. Matthei, MD.)

virilization (clitoromegally in females and excessive phallic development in males) [39]. This constellation of findings should result in an endocrine workup to distinguish among the various possible etiologies of this syndrome. The workup will include an ultrasound of the gonads and retroperitoneum [40] to localize any masses that would be responsible for the syndrome. In many instances, both adrenal glands are enlarged symmetrically, which is consistent with a diagnosis of Cushing's disease if seen in conjunction with an elevated corticotropin level. Upon administration of high-dose dexamethasone or metyrapone (a blocker of 11-β-hydroxylase), serum cortisol levels drop in these patients. Cushing's disease is caused by a corticotrophin-secreting pituitary adenoma, and is managed by neurosurgical techniques. The only other cause of elevated corticotropin in this setting is ectopic corticotropin secretion by another malignancy.

In the event that the corticotropin level is decreased, there may be non–corticotrophin-dependent bilateral hyperplasia (both adrenal glands should be enlarged equally), or there is an adrenal tumor that should be apparent on sonography or CT scan. Plasma cortisol levels in these instances are not suppressed by administration of either dexamethasone or metyrapone (as opposed to the suppression that is seen with Cushing's disease). These lesions are managed by surgical removal of the affected adrenal accompanied by a lymph-node sampling. In recent years, several groups have described a laparscopic approach to pediatric adrenalectomy [41]. It is critical to remember that an active adrenal tumor may induce contralateral adrenal suppression. This means that in the postoperative period, the patient may experience the signs and symptoms of adrenal insufficiency. This can be prevented with preoperative administration of hydrocortisone followed by a slow postoperative steroid tapering and monitoring of serum cortisol levels. It remains difficult for pathologists to determine whether these tumors are benign or malignant using histopathologic criteria. The presence of spread to the lymph nodes or adjacent or distant organs is the criterion by which malignancy is determined. In general, tumors less than 5 cm in diameter will be confined to the adrenal and are amenable to surgical cure [42].

Pheochromocytoma

Pheochromocytoma in the pediatric population is also extremely rare, and presents several challenges in diagnosis, medical, and surgical management that will be reviewed briefly. (The reader is referred to a recent review of pediatric pheochromocytoma management [43].) A bewildering array of presenting symptoms is possible for these patients. Flushing, headache, or the detection of hypertension in an emergency department or pediatrician's office often will trigger the workup. Rarely, these lesions will be present at other sites along the sympathetic chain; if near the bladder, patients have been reported to describe headaches with voiding. Several case reports describe patients presenting with strokes [44,45]. CT will localize most of these lesions, although more recent publications describe the use of positron emission tomography to identify nonadrenal sites [46]. These patients must be managed with alpha-blockers and simultaneous volume repletion in preparation for surgery [47]. This is critical because these patients are severely volume-depleted secondary to the vasoconstriction. Intraoperative fluctuations in blood pressure can be dramatic, and call for careful monitoring with an arterial line. A rapidly acting vasodilator, such as nipride, must be ready for use at any moment. Most of these lesions will be benign, and patients will recover fully after surgical removal. As with adrenal cortical tumors, there are no realiable histopathologic criteria to distinguish which lesions are malignant. These are defined by their metastatic spread, and although rare, usually are fatal [48].

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Pediatric urologic oncology: bladder, prostate, testis

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Although treatment for bladder, prostate, and testis cancer comprises a large part of adult urologic practice, the tumors that affect these organs in children are rare. Rhabdomyosarcoma, which affects the bladder, prostate, vaginal, and paratesticular areas, is treated with a combination of surgery, chemotherapy, and radiation. Most transitional cell carcinomas of the bladder and prepubertal testis tumors are managed surgically owing to the low stage at presentation. Application of the technical advances learned in adults with tumors of the bladder, prostate, and testis, combined with an understanding of the difference in tumor biology, helps urologists improve the treatment of these tumors in children.

Rhabdomyosarcoma

Although it is clear that a combination of surgery, chemotherapy, and radiotherapy is more successful than any single modality approach in the treatment of rhabdomyosarcoma, the optimal timing and dose of each method remain controversial. The urologist's experience with managing the complications of radiotherapy (proctitis, hemorrhagic cystitis, alterations in bladder function, irritative voiding symptoms) delivered for prostate adenocarcinoma in adults may predispose him or her to avoid radiotherapy if other alternatives are available, with the goal of preserving a comfortable child with a functional bladder.

When reading the literature on rhabdomyosarcoma, it is useful to remember three key points: (1) chemotherapy cures microscopic disease, (2) residual mass does not equal disease, and (3) radiotherapy renders pathologic specimens difficult to read. The incidence of rhabdomyosarcoma peaks between the ages of 2 to 4 years and 15 to 19 years, with 20% of rhabdomyosarcomas involving the bladder, prostate, vagina, or paratesticular area. In the United States, patients are managed by Children's Oncology Group Soft Tissue Sarcoma Committee protocols (formerly, the Intergroup Rhabdomyosarcoma Study Group [IRS]). Over the past 30 years, chemotherapy with vincristine, dactinomycin, and cyclophosphamide (VAC) has improved 3-year patient survival from a range of 40% to 73% to 86%, with a 77% rate of 3-year, failure-free survival [1]. During the same time, surgery has progressed from exenteration to organ preservation following chemotherapy, with an improvement in the functional bladder salvage rate from 25% to 60%. The latest trial, IRS-V, is studying new agents such as topotecan for advanced disease while lowering cyclophosphamide and radiation dosing for low-risk patients. Because of the ineffectiveness of high-dose chemotherapy followed by bone marrow transplantation in advanced disease, there are no plans to study this route any further [2,3].

Rhabdomyosarcoma consists of small blue round cells, similar to neuroblastoma, Ewing's sarcoma, non-Hodgkin's lymphoma, and leukemia. Embryonal pathology, which is favorable, accounts for 90% of genitourinary rhabdomyosarcomas. Sarcoma botryoides (''bunch of grapes'') is a polypoid form of embryonal pathology that occurs in hollow organs such as the bladder. Alveolar pathology, which tends to occur in extremities, is less favorable.

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Translocations between chromosomes 1;13 (favorable) and 2;13 (very high risk) are prognostic markers for survival in patients with alveolar tumors with metastatic disease [4]. For the more common and less aggressive embryonal tumors, there are no good prognostic molecular markers [3]. Although there may appear to be a pseudocapsule, the tumor is unencapsulated. Multiple biopsies are required to ensure that the excision is complete.

Evaluation

Bladder and prostate primaries have a 2.5 to 1 male predominance and tend to occur at the trigone and bladder neck. Presenting symptoms can include urinary retention, a palpable lower abdominal mass, gross hematuria, and constipation. In girls, the sarcoma botyroides can prolapse through the urethra. Although determining which organ the tumor arose from can be difficult, the initial treatment does not depend on this distinction. Properly performed biopsy and imaging will provide enough information to start treatment with chemotherapy. CT or MRI (T2 weighted) of the pelvis is the preferred initial study; MRI may give better resolution of tumor invasion.

Vaginal primaries occur on the anterior vaginal wall and present with vaginal bleeding or an introital mass. Uterine primaries can be treated successfully with limited excision followed by chemotherapy. Currently, hysterectomy is rarely performed [5]. Vulvar and cervical lesions tend to occur in teenagers [6]. CT or MRI (T2 weighted) of the pelvis is the initial study.

Endoscopic examination, bimanual pelvic examination under anesthesia, and biopsy of bladder, prostate, and vaginal primaries completes the local staging evaluation. Cold-cup biopsy will give better results than the resectoscope loop, because it avoids the cautery artifact that complicates pathologic interpretation. A submucosal lesion may require needle biopsy via a percutaneous transperineal or laparoscopic approach.

Paratesticular rhabdomyosarcoma has a bimodal peak, occurring in the 3- to 4-month-old boy and in the teenager. The neonatal tumor is more benign than the tumor presenting during the teenage years (90% versus 63% failure-free survival rate at 3 years) [1]. The primary tumor usually presents as a painless scrotal mass. To distinguish it from a testicular primary, scrotal ultrasound and serum assays for β-human chorionic gonadotropin (β-hCG) and alpha fetoprotein (AFP) should be performed. CT or MRI of the retroperitoneum is usually performed before surgery. Thirty percent to 40% of boys have microscopic metastases to the retroperitoneum. The tumor (and accompanying testis) is resected via a radical inguinal orchiectomy. A retroperitoneal lymph node dissection (RPLND) is currently recommended for all patients 10 years of age or older (regardless of radiologic findings) and in patients less than 10 years of age with retroperitoneal disease visible by imaging [3]. In boys under 10 years of age with negative retroperitoneal imaging, node dissection is not performed, because chemotherapy can cure microscopic disease [7].

A metastatic work-up for all lesions is completed with a chest radiograph (possibly chest CT), liver function tests, bone scan, and bone marrow biopsy.

Staging

The IRS studies include preoperative staging (Box 1) and postoperative grouping (Box 2) [1]. Use of the tumor, node, metastasis (TNM) system in preoperative staging in IRS IV-V has eliminated the bias present in IRS I-III, because patients are grouped based on the completeness of surgical resection (shifting patients from group 1 to group 3). Currently, about 80% of bladder and prostate

Box 1. Preoperative staging for rhabdomyosarcoma

T1: confined to organ of origin, a: ≤5 cm in size, b: >5 cm in size
T2: extension or fixed to surrounding tissue, a: ≤5 cm in size, b: >5 cm in size
No: regional nodes clinically negative
N1: regional nodes clinically positive
Nx: unknown
Mo: no distant metastasis
M1: metastasis present
Stage I: vaginal and paratesticular rhabdomyosarcoma, any T, any N, Mo
Stage II: bladder/prostate rhabdomyosarcoma, T1a or T2a, No or Nx, Mo
Stage III: bladder/prostate rhabdomyosarcoma, (T1a or T2a) and N1, Mo, OR (T1b or T2b), any N, Mo
Stage IV: any tumor with M1

Box 2. Postoperative grouping for rhabdomyosarcoma

Group 1: localized disease, completely excised, no microscopic residual
- A: confined to site of origin, completely resected
- B: infiltrating beyond site of origin, completely resected

Group 2: total gross resection
- A: gross resection with microscopic local residual
- B: regional disease with involved lymph nodes, completely resected with no microscopic residual
- C: microscopic local or nodal residual

Group 3: incomplete resection or biopsy with gross residual

Group 4: distant metastases

primaries are group 3 (gross residual), whereas 50% of nonbladder/prostate primaries are group 1 (complete resection), with approximately 20% in group 2 (complete gross resection, with microscopic or nodal tumor) and group 3 (gross residual), respectively [8].

Chemotherapy/radiation

Administration of VAC is the current standard chemotherapy. It has been shown to be as effective, cheaper, and less toxic when compared with vincristine, ifosfamide, and etoposide (VIE) and vincristine, dactinomycin, and etoposide (VAE) regimens [1]. The addition of doxorubicin or melphalan to standard chemotherapy has not been beneficial. In an effort to adjust treatment according to risk (Box 3), low-risk patients are currently randomized to receive VA or VAC, plus or minus radiotherapy in IRS-V. Intermediate-risk patients receive chemotherapy and radiotherapy and are randomized to VAC or VAC alternating with vincristine, topotecan, and cyclophosphamide. High-risk patients receive CPT-11 (irinotecan), VAC, and radiotherapy [3].

To date, hyperfractionated radiotherapy has not achieved better results than conventional radiotherapy [9]. In IRS-V, patients with group 1 embryonal pathology do not receive radiotherapy. In other patients, gross residual primary tumors receive more radiation than microscopic residual disease, and metastases are irradiated as well [3]. Surgery as a treatment of gross residual disease after chemotherapy is still an option in this protocol. At the Children's Hospital of Philadelphia, the approach is to reserve radiotherapy until the patient is free of all gross disease. This approach facilitates follow-up imaging and the interpretation of pathology.

Box 3. Risk stratification for rhabdomyosarcoma

Low: most vaginal, paratesticular primaries, embryonal primaries with gross total resection, no metastases

Intermediate: most bladder/prostate primaries, nonmetastatic embryonal, alveolar, or undifferentiated tumors with gross residual disease, metastatic embryonal tumors less than 10 years old

High: metastatic embryonal tumors more than 10 years old, metastatic alveolar or undifferentiated tumors

Surgery

Goals of the initial and subsequent surgery are different. During the initial procedure, the goal is to obtain adequate tissue for a definitive diagnosis and to stage the disease. If possible, one should remove the tumor without removing the affected organ, except in the case of paratesticular tumors. If excision is not possible, chemotherapy should be given with a plan for a second-look operation. At that operation, a biopsy is essential to confirm whether a residual mass is tumor. Because the tumor can involute more rapidly than the supporting stroma, gross residual masses may not contain any viable tumor. The goal of the delayed definitive operation is a good radical but pelvic organ–sparing operation. If microscopic residual disease is found, brachytherapy or external beam radiotherapy can be used. Exenteration is reserved for patients who have failed previous therapies and is now rarely performed.

In Europe, an alternate approach is to give primary chemotherapy without any attempt at initial local control (radiotherapy or surgery) and to design subsequent local therapy based on the initial chemotherapy response [10,11]. The outcome of this approach compared with the surgically more aggressive approach in the IRS is still pending.

Currently, there is debate concerning the malignant potential of matured rhabdomyoblasts (well-differentiated cells with low mitotic activity) [12,13]. Finding this pathology in a patient who has received as much chemotherapy as can safely be given (limited by toxicity to other organs) normally results in resection of the involved organ; however, if this would require destruction of a functional bladder, observation with frequent radiologic follow-up may be an option to consider.

Relapse

Although relapse after treatment is an ominous sign, the initial pathology continues to influence survival. The 5-year survival rate after relapse is 64% for botryoid embryonal, 26% for other embryonal, and 5% for alveolar or undifferentiated pathology. The chance of survival after relapse is also improved if the embryonal lesion had a lower stage at diagnosis: 52% for stage I, 20% for stage II-III, and 12% for stage IV [14].

Bladder/prostate

Improvement in the functional bladder salvage rate from 25% to 60% in IRS-III was achieved by intensifying radiotherapy and chemotherapy (dactinomycin, VP-16) after realizing that early exenteration was inappropriate. For microscopic residual disease, the dose of radiotherapy was 41 Gray; for gross residual disease, the dose was 50 Gray. Patients underwent a third operative evaluation at 24 weeks for possible exenteration [15]. One of the difficulties of radiotherapy is that the tumors tend to be located at the bladder neck, where a dose of even 41 Gray may significantly risk urinary continence. Conformal radiotherapy and brachytherapy are being tried to limit radiation toxicity [16]. The long-term risk of inevitably progressive radiation vasculitis as well as possible bony pelvis deformity in these children must also be considered. There is also a greater than 10% risk of secondary malignancy, often another sarcoma in the radiation field. During treatment discussions, the urologist should weigh whether preserving a bladder without an outlet is better than removing the bladder entirely [17,18].

The techniques used in partial cystectomy and radical cystectomy in adults are applicable to bladder rhabdomyosarcoma in children. A full retroperitoneal lymphadenectomy is not necessary, but any suspicious lymph nodes along the great vessels between the obturator fossa and the renal veins should be removed to determine the radiation fields if radiotherapy is necessary postoperatively. Multiple frozen section biopsy specimens of the bladder are obtained around the tumor. Alternatively, a staging procedure in which these biopsy specimens are obtained at the second-look operation to define the margins of the tumor may be helpful in planning the definitive resection. If the biopsy specimens are negative, and the nonencapsulated tumor can be removed with a 2- to 3-cm margin, a partial cystectomy can be performed. As is true in all partial cystectomies, the issue is the balance between cancer control and the function of the residual bladder. If the tumor extends down the urethra, the symphysis should be split to gain better access, because it is essential to remove the urethra to the midbulbar level. After distal dissection of the urethra is completed, the symphysis is closed with absorbable suture. With this improved exposure, it is possible to perform a nerve-sparing dissection, although the outcome in terms of potency has not been assessed to date. The placement of brachytherapy catheters for afterloading (to treat microscopic positive margins, if needed) should also be considered.

If the patient requires total cystectomy, the authors have placed Dexon mesh across the abdomen to hold the intestines out of the pelvis at the level of the sacral promontory. This maneuver limits the exposure of the bowel to the radiation field if postoperative radiation is required. Mesh placement is performed by initial attachment to the sacral promontory, wrapping it around the sigmoid; otherwise, the technique for total cystectomy is identical to that used in adults with transitional cell carcinoma. Because the tumor does not involve the anterior urethra, a full urethrectomy is not required. The final surgical decision is whether to proceed with continent urinary reconstruction at the same time. This procedure should be discussed with the patient and the parents before surgery, because it will determine how much bowel preparation will be necessary. The authors believe that, unless the patient is motivated and able to perform clean intermittent catheterization, the reconstruction should be delayed. A 2-year disease-free period usually indicates cure. In younger patients who are not ready to manage a urinary reservoir, the authors have either brought up the remaining bladder plate with the ureterovesical junctions intact as a vesicostomy, or performed low end–cutaneous ureterostomies, with the ureters placed side-by-side as a single stoma on the abdominal wall.

For tumors involving only the prostate, the technique used for the treatment of localized prostatic adenocarcinoma is applicable. Careful handling of the bladder neck and urethral stump is important for eventual continence, because all of these patients have already been treated with chemotherapy, and some may have been treated with radiation as well. The use of nerve-sparing procedures may preserve erectile potency.

Of the patients who maintained an intact bladder in IRS I-II, function (as assessed by a questionnaire) was normal in 73%; 8% had incontinence, and 9% had frequency and nocturia. Although overall renal function (diverted, partial cystectomy, intact bladder) was normal in 95% of patients (based on serum blood urea nitrogen and creatinine), 29% of the patients had abnormal renal scans, which was often caused by hydronephrosis in the setting of a urinary diversion [17]. In IRS I-III, more than 25% of the patients treated with partial cystectomy had complications of gross hematuria, bladder contracture, or incontinence. The risk of complications increased as the radiation dose rose over 40 Gray [18].

More recent outcomes show that 50% of patients are managed with biopsy, 37% with partial cystectomy, and 13% with prostatectomy. Embryonal pathology results in an 83% 3-year failure-free survival compared with a 40% rate for alveolar pathology. All patients with metastatic prostate disease have died [15].

Vagina/uterus

Most patients are successfully treated with primary VAC chemotherapy after an initial biopsy. A second biopsy 8 to12 weeks after chemotherapy is recommended. Pelvic lymph node dissection is not necessary. Vaginectomy or hysterectomy should only be considered for persistent disease after a complete course of chemotherapy [19]. Radiotherapy should only be used for persistent disease or relapse [19,20]. Rhabdomyoblasts on biopsy are evidence of chemotherapy response; therefore, further chemotherapy, instead of resection, is the proper treatment.

In the overall IRS I-IV experience, 42% of patients were treated with surgery and chemotherapy, 19% required additional radiotherapy, 21% were treated with biopsy and chemotherapy alone, and 12% were managed with biopsy, chemotherapy, and radiotherapy. The 5-year patient and failure-free survival rates were 82% and 69%, respectively [6]. In IRS-IV, only 19% of patients required wide excision of vaginal tumors [20]. Younger patients (aged 1–9 years) had a better survival rate than those 10 years of age or older (94% versus 76%) [6]. The experience of the International Society of Pediatric Oncology (SIOP) in Europe has been similar using intracavitary brachytherapy for local control rather than hysterectomy [21].

Paratestis

Owing to the 30% to 40% rate of microscopic retroperitoneal nodal involvement, all patients underwent RPLND in the initial IRS studies [1]. After it was shown that chemotherapy could treat microscopic nodal disease [7], RPLND was not recommended in IRS-IV for stage I disease with a normal CT of the abdomen and pelvis. This change led to a significant understaging of disease based on radiologic evaluation alone and a decrease in failure-free survival in patients aged more than 10 years (a less favorable group), because patients with negative CT scans did not receive radiation. Thirty percent of the patients who were clinically stage I and over 10 years of age required retreatment. Based on the results of IRS-IV, patients who are less than 10 years old, who have stage I disease, and who have a negative abdominal/pelvic CT are treated with VA (vincristine, dactinomycin) chemotherapy in IRS-V. All patients with stage I disease who are 10 years of age or older undergo RPLND regardless of the CT findings. Patients with group 2 tumors (positive lymph nodes on pathology) are treated with radiotherapy and VAC [22].

In addition to the normal technique for inguinal orchiectomy, it is important to show on frozen section of the proximal cord that there is no tumor. If one makes a scrotal incision for what turns out to be a solid paratesticular mass, chemotherapy will often cure residual disease in the scrotum, although some cases have required hemiscrotectomy owing to tumor infiltration. It appears that, for the most part, chemotherapy is successful in sterilizing tumor infiltration of the scrotum [23,24], and follow-up physical examination for scrotal wall recurrence is easily accomplished.

The technique for RPLND is identical to that used for retroperitoneal involvement by testicular tumors. Ipsilateral template, nerve-sparing techniques can be used to maintain ejaculation [25], but no study has yet evaluated the outcome of contemporary RPLND techniques on preservation of ejaculation in these patients.

The 3-year patient survival and failure-free survival rates were 92% and 81% for group 1 tumors in IRS-IV, respectively. The failure-free survival rate was worse than the 95% rate achieved in IRS-III, although the patient survival rate was the same (96%). This result was thought to be due to understaging when the retroperitoneal lymph nodes were not pathologically evaluated in older boys. Patients older that 10 years had only a 63% survival rate, leading to the recommendation that all patients aged more than 10 years undergo RPLND in IRS-V [1]. Surprisingly, in one European study, only 1 of 72 patients with negative CT scans was subsequently found to have surgically positive retroperitoneal lymph nodes. Nevertheless, patients older than 10 years of age were still more likely to have positive lymph nodes, leading to the recommendation for intensified treatment for this subgroup [23]. A large primary tumor size (>5 cm) was also found to be an adverse risk factor in the SIOP MMT 84 and 89 trials, and more intense chemotherapy was recommended [24].

Complications

Most patients have acute toxicity from the chemotherapy. Ninety percent had myelosuppression, 55% had significant infections, and 2% had renal toxicity [1]. Most relapses occur within 3 years of initial diagnosis [14]. Late recurrences can occur in patients who are treated with chemotherapy alone, supporting the concept of multimodal therapy. Of 883 patients, 10 had a secondary cancer. Patients with pre-existing renal abnormalities were more likely to die (5% versus 1%) [1]. In IRS I-II, there was a 27% long-term urinary complication rate, with incontinence being the major issue. Twenty-nine percent of patients required sex hormone replacement, and 11% were shorter than expected [17]. If radiotherapy is used, there is an increased risk for a secondary neoplasm, often another sarcoma, in the radiation field. Bony pelvic abnormalities of the hips and femurs are possible after radiation [26]. Complications specific to surgical treatment include intestinal obstruction, anejaculation, and lower-extremity edema after RPLND. Because these data reflect surgical practices from 1972 to 1984, current techniques may result in better outcomes [27].

Transitional cell carcinoma

Transitional cell carcinoma in children tends to be pathologic grade I, nonrecurring, and has an extremely low rate of progression [28]. Children with transitional cell carcinoma are often initially diagnosed by ultrasound, because the routine evaluation of hematuria in children does not include cystoscopy. Transurethral resection of the tumor with an appropriately deep muscle biopsy at the area of the tumor is performed. The authors do not routinely obtain multiple random biopsy specimens of the bladder, because transitional cell carcinoma in children does not behave like a field defect as it does in adults. The authors' practice has been to observe these children with ultrasounds after resection if the follow-up cystoscopy and biopsy are negative, because the natural history is usually benign.

Prepubertal testis tumor

These tumors peak in the 2- to 4-year-old age range, represent 1% to 2% of all pediatric solid tumors, and are rare in African-American and Asian populations. In general, they are more benign and have a better outcome than testis tumors in adults. Only 65% of prepubertal testis tumors are germ cell tumors. A history of trauma is often given, which probably alerts the boy to a previously unrecognized painless enlarged testis. Box 4 lists the distribution of pathologies in the 2002 American Academy of Pediatrics testis tumor registry [29]. Box 5 shows the staging system for testis tumor used by the Children's Oncology Group.

The predominance of yolk sac tumors may reflect a reporting bias, because, in the authors' experience as well as others [30,31], teratomas are more common but often not reported because they are benign. The evaluation of a prepubertal testis mass is similar to that of a tumor in an adult. Studies include scrotal ultrasound and assays for serum AFP and β-hCG levels. Because the AFP (a marker for yolk sac tumors) can normally be elevated in newborns and in patients

Box 4. AAP testis tumor registry, 2002

Yolk sac, 62%
Teratoma, 23%
Gonadal stromal, 4%
Epidermoid cyst, 3%
Juvenile granulosa, 3%
Sertoli cell, 3%
Leydig cell, 1%
Gonadoblastoma, 1%

Box 5. Staging for prepubertal testis tumor

Stage I: Local disease, complete resection, markers normalize
Stage II: Transscrotal orchiectomy, microscopic disease in scrotum or high cord (<5 cm from proximal end), <2 cm retroperitoneal lymph node, persistently elevated markers
Stage III: >2 cm retroperitoneal lymph node
Stage IV: distant metastases

with liver dysfunction, serial determinations after orchiectomy are needed. A chest radiograph should also be obtained, because metastases from yolk sac tumors are more likely to the lung than to the retroperitoneum. A CT scan does not need to be obtained until there is pathologic confirmation that the lesion is a yolk sac tumor.

The yolk sac tumor is managed with radical inguinal orchiectomy. The pathology will reveal Schiller-Duval bodies. Metastases to the lung occur in 20% of cases compared with 4% to 6% to the retroperitoneum. If the patient is stage I (no chest or retroperitoneal adenopathy, appropriate drop in AFP), no chemotherapy is necessary [29]. The surveillance program consists of monthly assays for AFP, chest radiography every 2 months for 2 years, and CT scans every 3 months for the first year and then every 6 months for the second year. Patients with stage II disease receive cisplatinum, etoposide, and bleomycin (PEB) but no radiotherapy, and can expect a 99% survival rate. Patients with stage II disease with a persistent mass or persistent elevated AFP after chemotherapy should undergo RPLND. Patients with stage III and IV disease should undergo chemotherapy and RPLND. Overall survival rates for all stages approach 100%.

Before puberty, the teratoma is the first or second most common testis tumor and can be managed with a testis-sparing approach [29,32]. It is always benign in the prepubertal patient, even when the pathology shows immature elements. A scrotal ultrasound showing internal calcifications and a heterogeneous mass in the testis in association with a normal AFP level should suggest teratoma. Intraoperatively, after vascular control has been obtained, the teratoma can be shelled out from the testis, and a frozen section can confirm the pathology. Almost all prepubertal testis tumors are of one histologic type, and the frozen section analysis is accurate. If maturational changes are seen in the seminiferous tubules, or if immature teratoma is seen on frozen section and the patient is entering puberty, the entire testis should be removed [29]. Today, most boys with a teratoma have good gonadal preservation after testis-sparing surgery.

Leydig cell tumors are the most common gonadal stromal tumors of adults and children [33]. The classic triad of findings in patients with Leydig cell tumors is precocious puberty (10%), a unilateral testis mass (90%), and an elevated level of 17-ketosteroids. Unlike in precocious puberty induced by a pituitary lesion (high luteinizing hormone [LH], follicle-stimulating hormone [FSH], and testosterone), Leydig cell tumors display a low LH and FSH and high testosterone. Leydig cell tumors can also be managed using a testis-sparing approach, because they are benign in children [32–34]. The Reinke crystal, which is pathognomonic for Leydig cell tumors in adults, is rarely found in children. Sertoli cell tumors are rare in children, usually benign, and safely treated with a testis-sparing procedure [32,33,35]. Follow-up is necessary for these tumors, because the pathology does not always predict outcome [33]. Gonadoblastoma is classically encountered in patients with mixed gonadal dysgenesis (45,X/46,XY) or in intersex with dysgenetic gonads in association with a Y chromosome in the karyotype. Although it is a low-grade malignancy, the gonad at risk is managed with early gonadectomy. Tumors are bilateral in a third of cases, can be malignant in 10%, and usually present after puberty [36].

Secondary tumors of the testis are usually caused by lymphoma or leukemia, and they appear hypoechoic on ultrasound. Most centers have stopped performing biopsies of the testes of patients who are completing chemotherapy for lymphoma and leukemia, because there has been no survival advantage [37]. If a patient has an enlarged testis after treatment for lymphoma or leukemia, a biopsy specimen of the affected testis should be obtained and testicular radiation given. Additional chemotherapy should also be given, because the presence of tumor in a sanctuary site such as the testis suggests residual disease elsewhere. The rare extragonadal germ cell tumor (retroperitoneal and abdominal) is best treated with initial biopsy (complete resection if possible), chemotherapy, and re-resection of residual tumor. The event-free survival rate is 83% at 6 years [38].

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The craft of urologic surgery: modern radical perineal prostatectomy

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Radical perineal prostatectomy (RPP) is the original approach used by urologists for removing the entire prostate for cancer treatment. From its original description approximately 100 years ago, it has gone through periods of increased and decreased popularity. RPP has not been performed as commonly in the United States since the late 1970s, with the introduction of the radical retropubic prostatectomy (RRP) and description by Walsh [1] of nerve sparing with this approach. With increased emphasis on reducing morbidity associated with radical prostatectomy by less-invasive techniques such as the laparoscopic prostatectomy, however, more surgeons are revisiting RPP as an alternative. As discussed in this article, this approach offers several advantages over the retropubic or laparoscopic approach for certain patients.

History of the radical perineal prostatectomy

Ammonius Lithotomous was the first person credited with performing surgery through the perineum when he described the removal of a bladder stone through the perineum in 400 BC [2]. In AD 25, Celsus developed a curved perineal incision to gain access to the bladder for removal of bladder stones. This eventually would become the basis for the incision used in the perineal prostatectomy today [2]. In 1639, Covillard reported the successful although accidental removal of a portion of the prostate during removal of a bladder stone through the perineum. He and several other surgeons through the seventeenth and eighteenth centuries used a median incision in the perineum rather than the curved incision described by Celsus [3].

Throughout the eighteenth and nineteenth centuries, several surgeons reported the removal of portions of the prostate similar to Covillard, but Guthrie performed the first planned prostate enucleation through a median perineal incision in 1834 [3]. This subsequently led to the use of the median perineal incision for the removal of prostatic carcinoma. In 1882, Leisrink adapted the Celsus curved incision for the perineal removal of prostate carcinoma followed by urethral reconstruction [2]. Most of this procedure, however, was performed "blindly." It was Billroth [4], in 1867, who first described the perineal prostatectomy for the treatment of prostate cancer in a professional journal.

One of the problems associated with performing the perineal prostatectomy in the late 1800s was the lack of visualization. In 1900, Syms developed a balloon to inflate in the bladder on which traction could be placed to pull the prostate down into the perineal incision [2]. Subsequently, in 1901 Proust reported changing the perineal prostatectomy from a blind procedure to a visualized procedure, using a prostatic retractor he developed [2]. In 1903, Young used the curved perineal incision to perform a prostatectomy for the removal of the entire prostate for benign prostatic hyperplasia [2]. Young stressed the importance of performing all portions of the

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procedure under direct visualization and developed such tools as the Young retractor and the perineal table to facilitate visualization (Figs. 1 and 2).

While performing prostate enucleations for benign prostatic hypertrophy, Young became interested in the spread of prostate cancer in the gland. Young performed a series of autopsies in men with prostate carcinoma to identify the pattern of cancer spread. This led him to believe that prostate cancer spread along the ampullae of the vasa to the seminal vesicles, and that the cancer usually was contained within Denovillier's fascia [5]. During this same period, Halsted was performing the radical mastectomy for the treatment of breast cancer. Together, Young and Halsted developed a radical operation to remove the prostate, the fascia of Denovillier, the seminal vesicles, ampullae of the vasa, and the vesical neck with a portion of the trigone, and thus performed the first "radical" perineal prostatectomy in 1904 [6]. In 1908, Young reported on 128 RPPs with no mortality, which was a drastic reduction from the 25% to 50% mortality seen with previous perineal prostatectomies. The RPP has undergone only minor modifications since Young described it.

One minor modification of Young's original procedure includes the use of chromic catgut rather than silk for the vesicourethral anastomosis to prevent stone formation on the suture [6]. Another modification was that initially, Young's prostatic

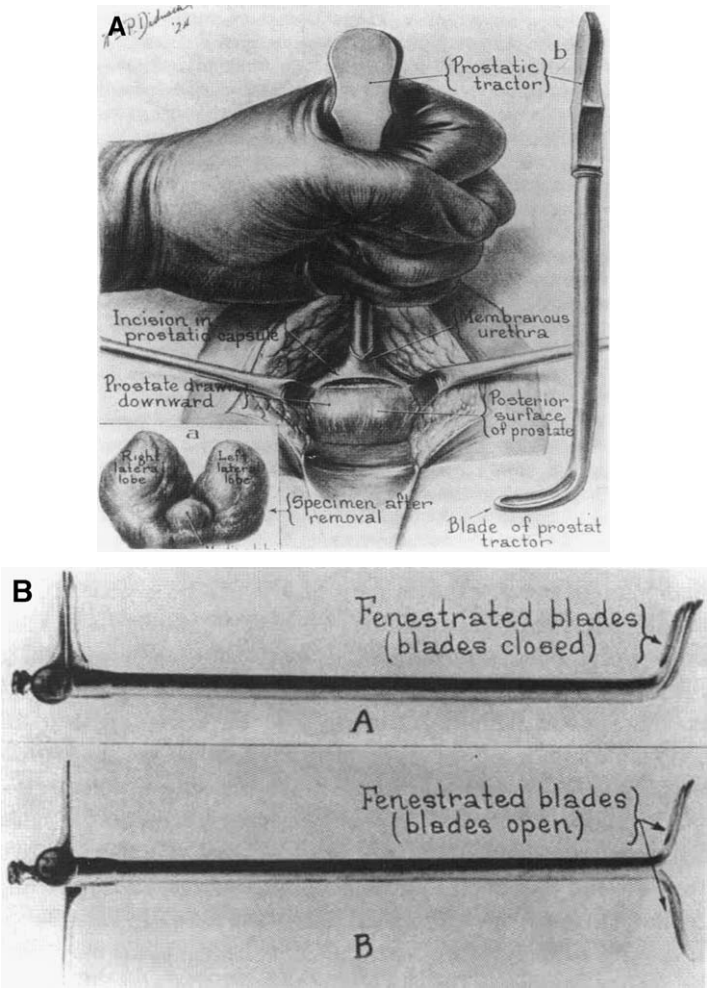

Fig. 1. (*A*) Young's original depiction of prostatic tractor used for enucleation of the hypertrophied lobes of the prostate. (*B*) The Young retractor. (Illustration from William P. Didusch; with permission.)

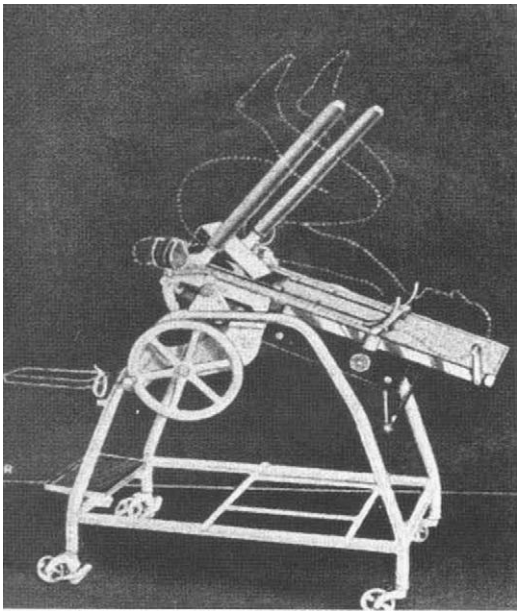

Fig. 2. The Young perineal table. (Illustration from William P. Didusch; with permission.)

retractor was inserted through an incision in the membranous urethra. Wildbolz recognized that this might lead to damage of the external urinary sphincter and thus described a technique to preserve the tissue surrounding the external urinary sphincter to reduce the incidence of urinary incontinence [2]. A third modification of Young's original RPP was the omission of pads or packs that were placed in the perineal wound for later removal. In 1928, Gibson [7] recommended that these pads be omitted during closure, which significantly decreased wound problems as well as fistula formation. In 1939, Belt [8] modified the Young RPP by approaching the prostate through the perineum between the longitudinal fibers of the rectum and the circular fibers of the external anal sphincter. Other modifications, however, such as leaving behind the apex of the prostate to achieve better urinary control, and opening the anterior layer of Denonvillier's fascia during the dissection, were believed by Young to violate the principles of cancer surgery, and he discouraged their use in RPP [6].

In 1945, Millin [9] popularized the technique of the RRP. His approach emphasized early division of the urethra and the removal of the entire prostate gland. Unfortunately, the significant blood loss associated with the retropubic approach discouraged many from its use. In 1959, Campbell [10] described an antegrade approach for the removal of the prostate to decrease blood loss by early ligation of the vascular pedicles, but blood loss remained significant. As a result of morbidity in the form of blood loss, incontinence, and erectile dysfunction, combined with the advent of radiation therapy, RRP and RPP fell out of favor [11,12].

Through the 1960s and early 1970s, literature began to accumulate on the morbidity associated with radiation, but it continued to play a significant role in the treatment of prostate cancer because of the significant morbidity, especially blood loss, associated with radical prostatectomy. Finally, in 1979, Reiner and Walsh [13] reported early meticulous ligation of the dorsal vein during RRP that greatly decreased the blood loss associated with the procedure. In addition, Walsh, after performing detailed anatomic dissections in the male pelvis, published the first description of the nerve-sparing RRP, leading to wide acceptance of this procedure for the treatment of prostate cancer [1].

With the decreased complication rates seen with RRP, fewer physicians were trained in the perineal approach. In recent years, however, there has been renewed interest in RPP for several reasons. First, the research of Weldon and Tavel [14] in the late 1980s demonstrated that nerve-sparing techniques also could be applied to the perineal approach. As discussed later, outcomes regarding potency between RRP and RPP have shown no statistical difference. Second, one criticism of the RPP was the inability to sample the pelvic lymph nodes, but with predictive models such as the Partin tables and the Kattan nomogram, patients at low risk for pelvic lymph node metastases can be identified, thus allowing for the safe exclusion of a pelvic lymph node dissection [15]. Third, with the stage migration seen in the United States in prostate cancer, fewer patients have lymph node involvement. Finally, with increasing attention on decreasing the morbidity of prostatectomy with techniques such as laparoscopic prostatectomy, the RPP has had a resurgence. In addition, as opposed to laparoscopy, long-term data on outcomes are available for perineal prostatectomy [16].

Patient selection

Patient selection is critical to performing a successful RPP. Practical considerations for patient selection include certain anatomic features, such as patient size. Obese patients typically have less subcutaneous fat on the perineum than in the

lower abdominal area, which often makes RPP a better approach than RRP. If the patient is morbidly obese, however, then the positioning required for RPP may pose a problem. To perform an RPP, the patient must be placed in an exaggerated lithotomy position (Fig. 3). This allows the perineum to be parallel to the floor, which is necessary for the proper dissection. In morbidly obese patients, this position may increase the ventilatory pressures to above 40 cm H_20, resulting in insufficient oxygenation. To help determine if a patient will be able to tolerate this positioning, the physician can have the patient lie supine on the examination table and bring his knees to his chest. If the patient is able to tolerate this test in the office, then he likely will tolerate the positioning required for RPP.

Another anatomic consideration for RPP is the depth of the patient's perineum. If the base of the prostate gland is not palpable on digital rectal examination, dissection during RPP may be difficult because of the depth of the wound; thus, these patients are poor candidates for RPP. Also, if the distance between the patient's ischial tuberosities is narrower than the prostate gland, perineal removal of the prostate can be difficult. In addition, prostates larger than 100 g are difficult to remove through the perineal approach. In these cases, one may consider downsizing the prostate with a luteinizing hormone–releasing hormone agonist before prostatectomy. Other patient characteristics that may exclude them from the perineal approach are hip ankylosis, severely limited hip mobility, and lower extremity amputations.

Because patients who undergo RPP do not have pelvic lymph nodes sampled routinely, patients at high risk for nodal metastases typically are not candidates for this approach. Some surgeons have combined laparoscopic pelvic lymph node dissections with RPP for patients at greater risk for lymph node metastases, and there is a recent report of performing a pelvic lymph node dissection through a perineal incision using laparoscopy [17]. The drawback of this approach is the increased operative time, as well as the expertise required to perform laparoscopic lymph-node dissection. Given the predictive models available, such as the Kattan nomogram and Partin tables, however, patients with a low probability of lymph node metastases can be selected [15]. Furthermore, with the stage migration seen in prostate cancer since the introduction of prostate-specific antigen (PSA) testing, patients can be selected accurately to undergo RPP with the exclusion of a pelvic lymph node dissection [18,19].

Advantages of radical perineal prostatectomy

Some characteristics of patients make them particularly well suited for RPP rather than a laparoscopic or retropubic approach. Typically, patients who have undergone previous pelvic surgery are excellent candidates for RPP. In particular, patients who have had meshed hernia repairs, renal transplantation, and pelvic/abdominal vascular bypass grafts are better candidates for the perineal approach than for the retropubic or laparoscopic approach because the perineal

Fig. 3. The exaggerated lithotomy position for radical perineal prostatectomy.

dissection is through virgin tissue. Furthermore, in patients who have had prior pelvic irradiation for their prostate cancer and undergo prostatectomy (salvage prostatectomy), the perineal approach has tended to be technically advantageous compared to RRP. Also, obese patients may be better candidates for the RPP approach.

Preoperative preparation

Because of the proximity of the rectal wall throughout the dissection, the authors routinely perform a mechanical bowel preparation and antibiotic prophylaxis on all patients. The bowel preparation includes a clear liquid diet the day before surgery, oral buffered sodium biphosphate (45 mL), and erythromycin and neomycin (1 g) as described by Nichols and colleagues [20]. Because the authors transfuse less than 1% of their RPP patients, blood type and cross, or type and screen testing usually is not performed. In addition, the authors do not recommend routine autologous blood donation to their patients because of cost and lack of need.

Technique

Incision

First, a Lowsely prostatic retractor is placed into the bladder through the urethra and the wings are opened. An inverted U- or horseshoe-shaped incision is made just inside the ischial tuberosities with the apex of the incision located 2 to 3 cm anterior to the anal verge; usually a color change in the skin denotes the proper location (Fig. 4). The incision is carried medial to the ischial tuberosities and posteriorly to a point lateral to the sphincter at the 3-o'clock and 9-o'clock positions. The incision can be carried further posteriorly without side effects if large flaps are needed. The incision is then carried down 1 to 2 cm into the subcutaneous fat.

The ischiorectal fossa is developed by making small stab incisions through the ischiorectal fascia bilaterally at the superior aspect of each vertical arm of the incision. Once a defect has been created, these spaces are developed bluntly with the index fingers directed inferiorly and perpendicular to the floor. The spaces are opened with electrocautery, and once adequately developed, the index fingers are brought together toward the midline. A space is then created under the central tendon connecting the ischiorectal fossae. This space overlies the anterior rectal wall and is superior to the anal sphincter. The central tendon is then divided with cautery (Fig. 5).

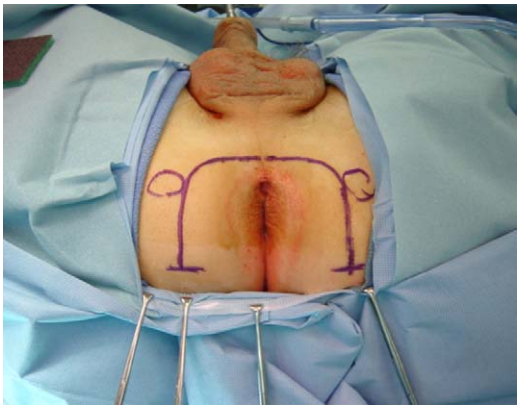

Fig. 4. Perineal incision.

Rectal mobilization

Once the central tendon has been divided, the rectal sphincter should be visible as an arch overlying the rectum. Dissection is then performed between the longitudinal rectal fibers on the ventral aspect of the rectal wall and the external anal sphincter. As described by Hudson [21], a modified Belt approach is used that creates bilateral spaces through the midportion of the sphincter with the remaining central tendon between the two (Fig. 6). This allows the external anal sphincter to be lifted up and away from the underlying rectum. Next, a Young prostatic bifid retractor is placed beneath the external anal sphincter and elevated superiorly. An index finger is placed into the rectum and used for downward traction. The remaining central tendon is incised sharply with Metzenbaum scissors.

Fig. 5. Central tendon.

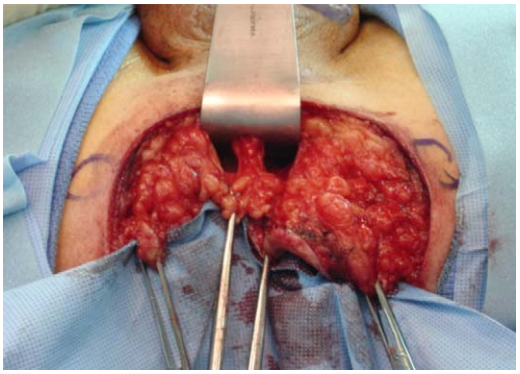

Fig. 6. Belt approach.

The longitudinal fibers of the rectum are followed to the rectourethralis muscle, which attaches the rectum to the posterior urogenital diaphragm. The finger placed in the rectum controls the depth of the dissection to prevent rectal injury. Blunt dissection to the level of the apex is performed on either side of the rectourethralis. The rectourethralis is developed variably, ranging from a few rudimentary fibers to a substantial fibromuscular structure several centimeters long. The rectourethralis now should be divided sharply because blunt dissection will result in rectal injury.

Next, a Thompson perineal retractor is placed (Fig. 7). The white and shiny ventral rectal fascia should be visible. The space between it and the rectal wall should be developed, which usually can be done with gentle, blunt finger dissection. The plane of dissection changes at this point to the vertical from the horizontal. The space must be developed to the base of the prostate, which is identified by palpation of the wings of the retractor. The rectal wall then is retracted gently with a padded retractor to provide optimum exposure.

At this point, the decision to proceed with nerve-sparing versus wide dissection must be made. The posterior lamella is the key, and how it is handled will define each technique. If a nerve-sparing technique is used, the fascia should be incised vertically, and the neurovascular bundles mobilized. If extended dissection is intended, the fascia is opened transversely at the level of the membranous urethra and the base of the prostate, if possible, freeing the rectum. Then the neurovascular bundle is ligated at its superior ends, and the dissection continued laterally to the base of the bladder.

Nerve-sparing approach

With the nerve-sparing technique it is crucial to understand that the dissection is performed in a different plane than the extended approach. To preserve the neurovascular bundles, the plane of dissection must be within the ventral layer of Denonvillier's fascia. With the rectum mobilized, the neurovascular bundles can be seen running within the lateral aspect of the ventral layer of Denonvillier's fascia. If a bilateral dissection is to be performed, a vertical incision should be made

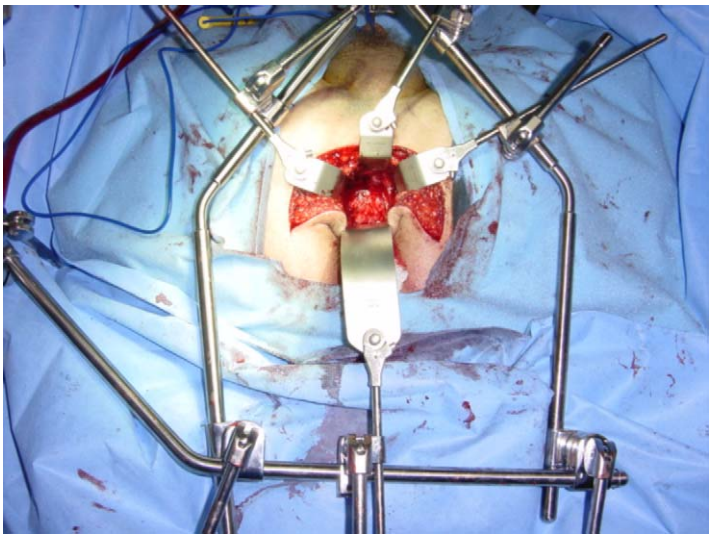

Fig. 7. Thompson perineal retractor.

in the midline. If a unilateral dissection is intended, the incision should be made 1 cm lateral to the midline on the side to be saved. The medial edge of the divided fascia then is elevated carefully and separated from the underlying prostatic capsule. Perforating vessels usually found entering the prostate from the neurovascular bundles at the superior and inferior neural pedicles are ligated with clips. The neurovascular bundles must be mobilized at least 1 cm over the membranous urethra and sufficiently proximal to the base to ensure enough laxity to avoid traction injury during removal of the gland. The dissection is continued laterally and ventrally on the prostatic capsule beneath the dorsal venous complex.

Using a combination of blunt and sharp dissection, the junction of the membranous urethra and apex of the prostate becomes apparent (Fig. 8). The urethra is surrounded by a right-angle clamp, and partially transected with a scalpel. 2-0 Monocryl (Ethicon, Somerville, New Jersey) sutures are preplaced at the 4-, 6-, and 8-o'clock positions. The Lowsley retractor then is removed and the remainder of the urethra sharply transected. The Young prostatic retractor is placed through the open prostatic urethra directly into the bladder and the blades extended.

Puboprostatic ligament division

Using the Young retractor, the prostate is rotated ventrally, which exposes the anterior prostatic capsule and the puboprostatic ligaments that lie in the midline beneath the dorsal venous complex. To avoid a positive apical margin, the ligaments are divided sharply to prevent tearing the prostate capsule from traction. Dissection is carried back along the prostate until the circular fibers of the bladder neck can be seen readily. If bleeding from the dorsal venous complex is encountered, the offending vessels can be grasped with vascular forceps and cauterized. For mild oozing, an open gauze sponge is placed against the plexus and compressed with a retractor until the prostate is removed. This bleeding usually stops after removal of the prostate.

The muscles of the bladder neck typically are visualized easily and transected with Thorek scissors. In lower-stage disease, wide excision usually is not performed. The anterior bladder neck is transected by cutting down onto the Young retractor until urine begins to flow out of the incision. The Young retractor is removed and traction applied with a 0.375-inch Penrose drain that is passed through the division between the base of the prostate and the bladder neck and brought out through the apex of the prostate using a right-angle clamp (Fig. 9). The posterior bladder neck is divided using Thorek scissors. The vascular pedicles, which serve as the primary attachments that restrict mobilization of the gland, are isolated carefully with a right-angle clamp and ligated with right-angle clips. Care must be taken to avoid the overlying neurovascular bundles if a nerve-sparing technique was performed.

Seminal vesicle dissection

At this point, the prostate should be anchored only by the seminal vesicles and ampullae of the vas deferens. An Alice clamp is placed through the prostatic urethra and clamped to the edge of the prostate to provide better posterior exposure. The prostate then is elevated anteriorly and the seminal vesicles approached posteriorly. The respective ampullae and seminal vesicle are isolated, ligated with surgical clips, and transected. The

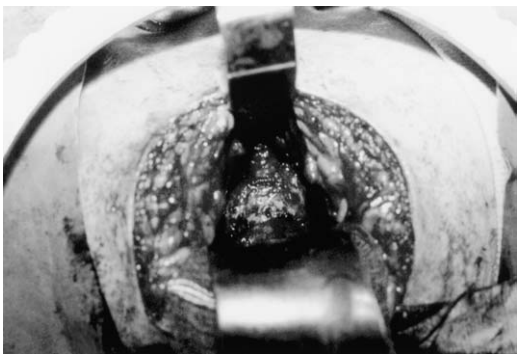

Fig. 8. Apex of prostate and membranous urethra.

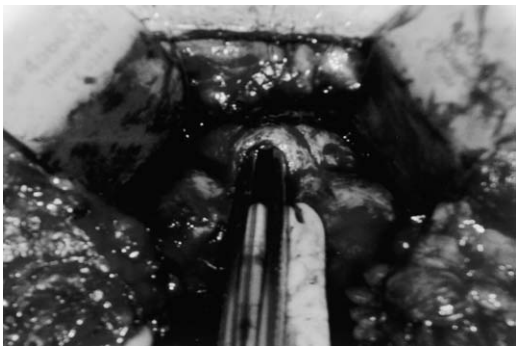

Fig. 9. Young retractor and Penrose drain.

prostate is now handed off the surgical field and the anastomotic repair begun.

Vesicourethral anastomosis

The bladder neck is inspected carefully for evidence of residual prostatic tissue, which is removed as needed. A 20-F Silastic catheter is placed in the urethral stump, and 2-0 Monocryl sutures are placed into the urethral stump at the 10-o'clock and 2-o'clock positions and into the anterior bladder neck at the corresponding positions. The catheter is advanced into the bladder. Any redundant posterior bladder neck is closed vertically in a racquet-handle technique with interrupted 2-0 chromic sutures. Because of excellent exposure and direct visualization it is unnecessary to evert the mucosal edges before anastomosis. The preplaced posterior sutures are placed through the bladder neck. The anastomosis is completed by tying all sutures down in a sequential fashion, beginning anteriorly and ending with the posterior sutures.

Closure

Because unrecognized rectal injuries are associated with significant morbidity, the authors routinely place a finger in the rectum before closure to ensure there are no incidental proctotomies. If encountered, proctotomies should be repaired using a standard two-layer closure with 3-0 Vicryl sutures (Ethicon, Somerville, New Jersey) for the mucosa and 3-0 silk Lembert sutures for the seromuscular layer. A 0.625-inch Penrose drain is placed anterior to the rectal surface and brought out through one of the corners of the incision. The wound is then closed in three layers. The perineal body is reconstituted connecting the deep and superficial portions of the muscle with 2-0 chromic sutures. The subcutaneous perineal fascia is closed with interrupted 2-0 chromic sutures and the skin edges approximated with 2-0 chromic horizontal mattress sutures. The sutures should be kept on the outside of the wound. Leaving suture tails of approximately 2.5 cm minimizes patient discomfort from the sutures. This closure provides more support at the apex of the wound where a breakdown is likely to occur.

Complications

Rectal injuries occur more frequently in RPP than in RRP [22,23]. The experience of the surgeon plays a role in the frequency of rectal injuries, with low rectal injury rates reported by surgeons experienced in RPP [16]. Rectal injuries usually occur as the rectourethralis is divided or as the plane of dissection changes from vertical to horizontal just before the apex of the prostate. If noted during surgery, these injuries are not problematic. The rectal injury typically is closed in two layers, with absorbable suture (such as 3-0 Vicryl) for the first layer followed by 3-0 silk Lembert sutures for the second layer. The surgical field is irrigated copiously with 1 L of antibiotic irrigation, and two-finger anal dilation is performed to reduce sphincter tone. Broad-spectrum antibiotics are given for 48 hours and a low-residue diet encouraged for 5 days postoperatively.

Recently, Bishoff and colleagues [24] reported a surprisingly high incidence of fecal incontinence after RPP. In this study, patients were mailed a questionnaire asking about fecal and urinary incontinence. Up to 16% of patients reported some fecal incontinence, with 3% reporting daily fecal incontinence. Up to 8% of patients who had undergone RRP also reported fecal incontinence. One shortcoming of this study was the lack of a validated quality-of-life questionnaire for prostate cancer. In 2003, Dahm and colleagues [25] reported on 78 patients who underwent RPP and were evaluated for bowel dysfunction using a validated questionnaire. This study demonstrated an increase in fecal incontinence and bowel dysfunction in relation to baseline, but these symptoms resolved in the early postoperative period.

The authors' experience has not been consistent with Bishoff's report, and they therefore reviewed data from the CaPSURE database to examine the incidence of bowel dysfunction after RRP and RPP. This study showed no significant difference in the incidence of bowel dysfunction between RRP and RPP, and that bowel dysfunction was not a significant problem (G. Hanson, MD and colleagues, unpublished data, 2004).

One complication unique to the positioning required for RPP is lower-extremity neuropraxia, the etiology of which is presumed to be undue pressure on the peroneal nerve caused by positioning. In 1998, Price and colleagues [26] reported that 23 of 111 patients (21%) undergoing RPP experienced some degree of lower-extremity neuropraxia. Fortunately, these cases of neuropraxia were of short duration (2–3 days) and all

resolved. A more recent study that evaluated 98 RPPs performed in 2001 revealed that 25.5% had transient neuropraxia [27]. Since 2000, the authors have used the Yellofins stirrups (Allen Medical Systems, Acton, Massachusetts) (Fig. 10) and have not seen this complication again. The stirrups support the entire leg from the calf to the foot in a boot-like support, minimizing pressure on the fibular head and ankle, which prevents the neuropraxia.

Other short- and long-term complication rates between RRP and RPP are similar, except for the need for blood transfusion, which is lower in the RPP group [22,28–30].

Outcomes

Most comparisons of outcomes have been between perineal prostatectomy and the radical retropubic approach, although recently comparisons between RPP, RRP, and laparoscopic prostatectomy have appeared. One of the first published reports directly comparing retropubic versus perineal prostatectomy was from Boxer and colleagues [28] in 1977. This study of 329 patients examined several variables, including mortality resulting from the procedure, overall survival rates, incontinence, and long-term complications. These authors found no significant differences between the two groups in the variables examined, except for an increased blood loss of 700 mL in the retropubic group. This study was a poor comparison for efficacy because many patients in the study had received estrogen therapy pre- or postoperatively. In addition, only 20% of the patients had undergone pelvic lymphadenectomies, leading to staging inaccuracies and difficulties in comparing the true cancer control rates of the two techniques.

Fig. 10. Yellofins stirrups.

Margins

Several series have compared the incidence of positive margins between RRP and RPP. In a study by Frazier and colleagues [29] that compared 122 patients who underwent RPP versus 51 patients who underwent RRP, there was no significant difference in positive margin rates between the two groups. A smaller study by Haab and colleagues [30] compared 71 patients who underwent RRP (36 patients) or RPP (35 patients) for clinically localized cancer of the prostate. In this study, patients were matched by their preoperative data including PSA level, clinical stage, and grade. Again, no statistically significant difference was found in the number of positive margins between the RPP and RRP groups.

A more recent article by Boccon-Gibod and colleagues [31], however, compared the incidence of positive surgical margins in patients undergoing RRP versus RPP. Ninety-four patients (48 RRP and 46 RPP) with clinically localized prostate cancer were reviewed retrospectively. The patients were stratified according to clinical stage, extracapsular extension with and without positive margins, and iatrogenic positive margins (incision into the prostate). These authors reported a 56% incidence of positive margins in the perineal group versus 61% in the retropubic group. Biochemical recurrence rates at a mean follow-up of 25 months were the same for each group (33%). Surprisingly, the incidence of positive margin rates in patients with pT2 tumors was significantly higher in the RPP group (43% versus 29%, $P < 0.05$). In addition, the incidence of iatrogenic margins was dramatically higher in the RPP group (90%) versus the RRP group (37%, $P < 0.05$). Their conclusion was that RRP is a better approach for the treatment of prostate cancer because it affords a lower likelihood of capsular incision. Despite the reported incidence of positive margins, biochemical recurrence rates were the same. A criticism of this study is that it was performed by surgeons without a great deal of experience with the RPP technique. In other studies using data from surgeons with significant experience in RPP, positive margin rates and iatrogenic positive margin rates are similar to those reported for RRP [29].

The largest comparison trial is that of the Uniformed Service Urology Research Group [22], a pooled analysis of data from five military installations of 1698 men who had undergone radical prostatectomies between 1988 and 1997. Of this group, 1382 underwent RRP and 316 underwent RPP. Again, there was no statistically significant difference between positive margins in the RRP and RPP groups. A recent study investigated the incidence of positive margins among RRP, RPP, and laparoscopic prostatectomy [32]. The focus of the study was 371 patients with organ-confined tumors out of 538 patients who underwent radical prostatectomy. Of the 371 patients, 116 had an RRP, 86 had an RPP, and 169 had a laparoscopic approach; positive margins were found in 22 (18.9%), 12 (13.9%), and 32 (18.9%) of the patients, respectively. A subanalysis revealed that each approach had a specific site where positive margins were most common: the apex for RRP, the bladder neck for RPP, and posterolaterally for laparoscopic prostatectomy. Overall, the data suggest that there is little difference among the approaches in terms of margin positivity.

Blood loss

Less controversial is the issue of blood loss. In almost all studies, the estimated blood loss was significantly less for RRP versus RPP [22,28–31]. Increased blood loss has ranged from 700 to 1400 mL for the RRP group and 170 to 800 mL for the RPP group with an average of 500 mL or less. A recent analysis from the Center for Prostate Disease Research database, which examined 2918 radical prostatectomies performed between 1985 and 2000, demonstrated that recently the estimated blood loss associated with RRP has decreased significantly [33]. Nonetheless, the transfusion rates and estimated blood loss generally is less with RPP.

A recent report by Tewari and colleagues [34] compared blood loss between radical robotic laparoscopic prostatectomy (RRLP) and RRP and found an average blood loss of 910 mL for RRP and 153 mL for RRLP. There were no transfusions in the group that received RRLP. Although no direct comparisons between blood loss in laparoscopic prostatectomy versus RPP exist, the reported blood loss for both is low, and there is no difference in the need for transfusion.

Continence

Completed studies also demonstrate no significant difference in continence [22,27–30]. A recent study by Young and colleagues [35] reported that at 12 months after RPP 66% to 84% of patients had returned to baseline urinary function and bother scores, as assessed by a validated questionnaire. This result compares favorably to the 56% to 71% return to baseline urinary function and bother scores for RRP reported by Litwin and colleagues [36]. Overall, as concluded by Gray and colleagues [37], there is little difference in terms of continence between RRP and RPP, and this factor should not influence the approach necessarily. Comparison studies to laparoscopic prostatectomy are lacking.

Erectile function

One of the main reasons for the increase in the number of RRPs performed was Walsh's description of nerve-sparing RRP [1]. It was several years before Weldon and Tavel [14] described the technique of nerve sparing during RPP. Despite this delay, the Uniformed Service Urology Research Group study, the largest study to compare outcomes between RRP and RPP, found no significant difference in the return of erectile function between the RRP group and the RPP group [22]. In the study by Frazier and colleagues [29], 77.3% of patients who underwent bilateral nerve sparing were reported to be potent after surgery. Unfortunately, no data on the potency rates in the RRP group were available, making a direct comparison impossible. The recent Tewari article [34] suggests that the time until the return of erections and intercourse is shorter with RRLP than with RRP. No published literature compares time to return of erections between RPP and RRLP or laparoscopic prostatectomy.

Biochemical recurrence

Unlike laparoscopic prostatectomy, long-term data are available on the incidence of biochemical recurrence for perineal prostatectomy. In the study by Haab and colleagues [30], when patients were matched for preoperative data including PSA level, the biochemical recurrence rates for the RPP group were not significantly different from the RRP group. Even in the study by Boccon-Gibbod and colleagues [31] that suggested higher positive margin rates in the RPP group, no difference in the rates of biochemical recurrences was noted. Recent shorter-term data examining

Table 1
Comparison of radical retropubic, radical perineal, laparoscopic, and radical robotic prostatectomy

Variable	RRP	Laparoscopic	RRLP	RPP
No.	100	50	100	50
Operative time	164 min	248 min	140 min	150 min
Blood loss (mL)	900	380	< 100	500
Margin pos (%)	24	24	5	10
Complications	15%	10%	5%	2%
Catheter days	15	8	7	10
Hospitalization days	3.5	1.3	1.2	1.5
5-y biochemical-free survival	—	—	—	90%

Data from Han M, Nadler RB, Catalona WJ, et al. Radical prostatectomy: should the retropubic approach remain the standard of care? Contemp Urol 2004;16:38–58 [41].

actuarial 3-year recurrence-free survival rates in patients with a PSA level less than 10 ng/mL who underwent either the RRP, RPP, or the laparoscopic approach found no significant differences among the groups (89.3%, 89.2%, and 86.2%, respectively) [38]. As with many other forms of therapy, however, longer-term follow-up may be necessary to see differences in biochemical failure rates.

Other

Other potential advantages of RPP over RRP are decreased postoperative pain, hospital stay, and time to return to work. Although there has not been a prospective comparison of these outcomes with RRP and RPP, Weizer and colleagues [27] prospectively evaluated pain medication requirement, time to unassisted ambulation, and return of bowel function. In this study, the average time to begin solid food was 21.2 hours, and time to unassisted ambulation was 22.4 hours. In addition, the patients had low narcotic requirements. There was a delay in return to ambulation and bowel function in patients who required a pelvic lymph node dissection during RPP, however.

A study of morbidity after laparoscopic radical prostatectomy found similar results, reporting that median time to ambulation was 1 day and 98% of patients began oral intake by postoperative day 2 [39]. Recent studies of pain medication requirements, time to oral intake, and unassisted ambulation of RRP are also similar between these two groups. Therefore, there seems to be little difference among the approaches in terms of short-term morbidity. Table 1 compares outcomes among the RRP, RPP, RRLP, and laparoscopic approaches.

Resident instruction

One concern regarding perineal prostatectomy is that it is a more difficult approach to learn. Mokulis and Thompson [40] studied this matter in a group of chief residents. Using operative time, estimated blood loss, transfusion requirements, and postoperative stay as surrogate markers for ease of the operation, they demonstrated that RPP was learned more quickly than the retropubic approach [15]. The only significant complication particular to learning the perineal approach was rectal injury. All rectal injuries were closed primarily at the time of RPP, however, and resulted in no long-term sequelae. This study contradicts the commonly held belief that the perineal approach is more difficult to teach and learn.

Summary

RPP is a surgical technique that has stood the test of time with only a few technical modifications since its original description by Young. Outcomes between RRP and RPP are similar, and seem to be similar compared to laparoscopic prostatectomy as well. RPP is the optimal approach for obese patients, patients with prior pelvic surgery, or patients with prior pelvic radiation. Proper patient selection, a detailed understanding of the perineal anatomy, and surgeon experience are crucial to the success of the procedure and the minimization of complications. For the experienced surgeon, RPP is an attractive option for the selected patient with localized prostate cancer.

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